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VOLUME 84 March, 1947 NUMBER 3

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1. Watson, E. P.: *J. Clin. Endocrinology* 4:571 (Dec.) 1944.

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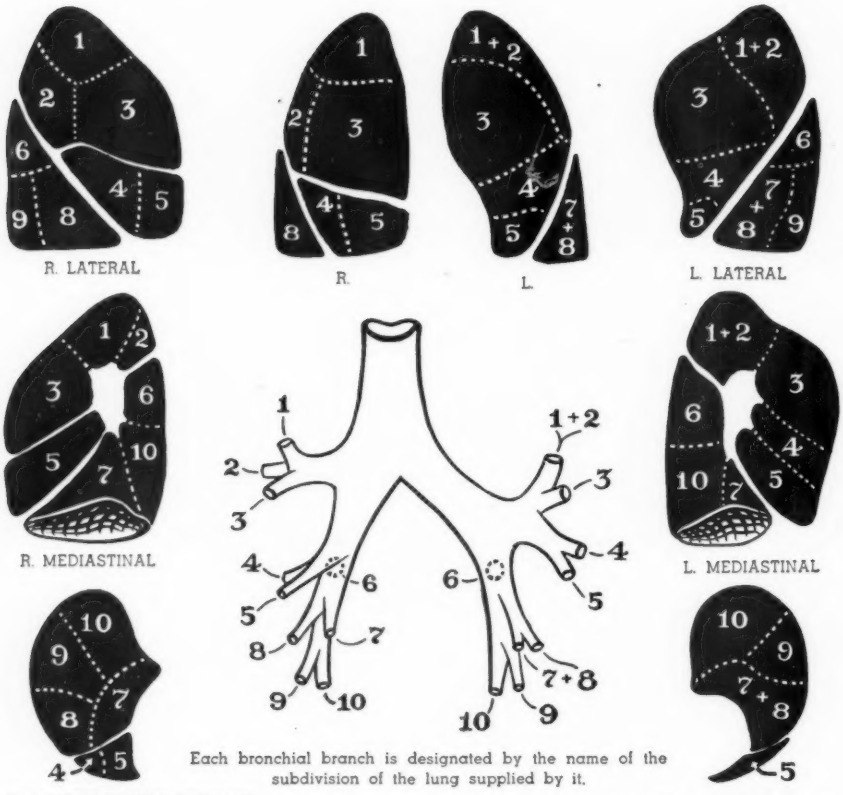
NOMENCLATURE FOR THE BRONCHI AND LUNGS

Adapted from
CHEVALIER L. JACKSON and JOHN FRANKLIN HUBER
Temple University School of Medicine



Each bronchial branch is designated by the name of the subdivision of the lung supplied by it.

RIGHT LUNG

LOBES	SEGMENTS	
Upper	Apical	1
	Posterior	2
	Anterior	3
Middle	Lateral	4
	Medial	5
Lower	Superior	6
	Medial Basal	7
	Anterior Basal	8
	Lateral Basal	9
	Posterior Basal	10

LEFT LUNG

LOBES	SEGMENTS	
Upper	Upper Division — Apical-posterior	1&2
	Upper Division — Anterior	3
	Lower (Lingular) Division — Superior	4
	Lower (Lingular) Division — Inferior	5
Lower	Superior	6
	Anterior-medial Basal	7&8
	Lateral Basal	9
	Posterior Basal	10

Fig. 1

A New Technique for Pulmonary Segmental Resection —Richard H. Overholt.

SURGERY
GYNECOLOGY AND OBSTETRICS

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A NEW TECHNIQUE FOR PULMONARY SEGMENTAL RESECTION

Its Application in the Treatment of Bronchiectasis

RICHARD H. OVERHOLT, M.D., Boston, Massachusetts, and LAZARO LANGER, M.D., Cordoba, Argentina

DOCTORS are confronted with few problems that are more serious than those presented by a patient suffering from bronchiectasis. The disease process, if untreated, is irreversible, progressive, and for most patients eventually causes death. On the other hand, of all chronic pulmonary diseases, bronchiectasis is one of the most hopeful for the reason that pulmonary resection affords not only alleviation of symptoms, but also cure in a high percentage of cases.

Although the fundamental pathology of primary bronchiectasis has been known for decades, only in recent years has the characteristic distribution of the disease in bronchopulmonary segments been realized. The increasing use of bronchography and the detailed study of surgical specimens have shown that bronchiectasis is primarily a segmental disease and rarely involves an entire lobe. In addition, bronchiectasis tends to involve the bronchopulmonary segments in certain patterns. Basal segments of the lower lobes are most commonly involved. The lingula division of the left upper lobe and the bronchi of the right middle lobe are frequently found to be diseased along with the basal segments. The superior segment of the lower lobe, however, is rarely affected. Another very important pathological and clinical observation has been that the distribution of primary bronchiectasis, as far as the affected segments are concerned, has usually reached its full extent at the time of diagnosis. Any progression of pulmonary involvement from this point on will not be through involvement of other segments by the bronchiectatic process, but by associated suppurative changes in the pulmonary parenchyma itself.

In recent years, many excellent anatomical studies (2, 3, 4, 6), along with increased surgical experience in resecting pulmonary tissue, have demonstrated that the bronchopulmonary segment is a surgical unit and lends itself to removal without undue technical difficulties or risk. As a result, segmental resection is now being used by us with increased frequency in the surgical treatment of bronchiectasis. Segmental resection not only eradicates all of the diseased segments, but it also eliminates the necessity of a sacrifice of uninvolved segments. This approach to the problem permits the accomplishment of two fundamental principles of surgery: (1) cure of the patient; (2) the preservation of as much functional tissue as possible.

During the past year we have developed a surgical technique which facilitates the removal of any bronchopulmonary segment. The use of clamps on lung tissue has been elim-

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inated. Damage to healthy segments is avoided. The intersegmental plane is dissected so as to ensure removal of all diseased bronchi.

The purpose of this paper is to describe an original and new technique of segmental resection. We wish to refer to its application in 23 cases of bronchiectasis.[1]

IMPORTANCE OF SEGMENTAL RESECTION

Bronchiectasis is primarily a segmental disease and frequently bilateral. It usually involves certain bronchopulmonary segments within the lobe rather than an entire lobe. Unisegmental disease is found less frequently than unilateral multiple segmental disease. It is also less common than bilateral involvement. In the last one hundred consecutive cases of primary bronchiectasis studied by us, 85 per cent were multiple segmental and in 30 per cent the disease was bilateral. In our series, the lower division of the left upper lobe (lingula) was involved in about 60 per cent of those patients whose principal disease was in the left basal segments. On the right side the middle lobe was found to be involved with the right basal segments in 45 per cent of our cases. A frequent bilateral pattern to be found shows involvement of the right middle, the lower divisions of the left upper (lingula), and both right and left basal segments.

Clinical observations have shown that the severity of symptoms is closely related to the amount of tissue damaged. Experience also has demonstrated that good end-results parallel the surgeon's ability to eradicate all portions of lung that are diseased. If entire lobes are considered as surgical units, serious respiratory embarrassment will result if the disease is completely removed in bilateral cases; for example, the removal of the right middle lobe, both lower lobes, and lower divisions of the left upper lobe, leaves the patient with one complete and one partial lobe which may not be sufficient for anything more than an invalid existence.

[1]Segmental resection is also being used for other localized conditions. Up to the present time this technique of segmental resection has been carried out in chronic lung abscesses (4 cases), hamartoma (1 case), metastatic mixosarcoma (1 case), and pulmonary tuberculosis (4 cases). The individual resection of the posterior and apical segments of the upper lobe, the superior of the lower, the posterior basal of the lower and the anterior of the upper were involved.

BRONCHIAL NOMENCLATURE

Bronchial nomenclature is far from being standardized. Various names for the bronchopulmonary segments have been suggested. This lack of standardization has led to much confusion. Jackson and Huber[2] emphasized the need for "terminology which will be acceptable to the bronchoscopist, the thoracic surgeon, and the radiologist and which will meet the approval of the anatomist." They have proposed a nomenclature now widely accepted which has been used herein (Fig. 1).

PRACTICAL CONSIDERATIONS

The conception that a bronchopulmonary segment be considered as a surgical unit is gaining greater acceptance. Nelson called attention to the pathological significance of certain segments and called the lingula the left middle lobe (counterpart of the right middle). He subdivided the lower lobe into two principal divisions: the dorsal (superior), and basal. He found that, anatomically, each segment possesses independent bronchovascular structures and is separated from the adjacent pulmonary tissue by an avascular plane. From time to time, thoracic surgeons have found it necessary to remove a part of a lobe by the use of clamps and multiple sutures. Most frequently, this technique was practiced in treating left lower lobe bronchiectasis with involvement of the lingula. The indurated lower tip of the upper lobe would be excised without precise dissection. Churchill and Belsey and Blades (1) have called attention to the importance of the removal of the lingula and other segments in the treatment of bronchiectasis and other diseases.[3]

Boyden has pointed out that, from a practical standpoint, most of the segments can be considered to be surgical units, but not strictly bronchovascular units. He found some arteries, mainly in the upper lobes, to be intersegmental and the veins to drain blood from adjacent segments.

[2]As a common basis for the choice of names, they have taken the position of the segment on the lobe. Terms like apical, basal, and lingula are unanimously recognized as part of the lung; anterior and posterior, superior and inferior, and medial and lateral indicate the position of the segments within the lobe.

[3]Since this manuscript was submitted for publication Clagett and Deterling in *Journal of Thoracic Surgery*, 1946, 15: 227-238, have discussed the importance of lingulectomy in bronchiectasis and describe a technique for its removal.

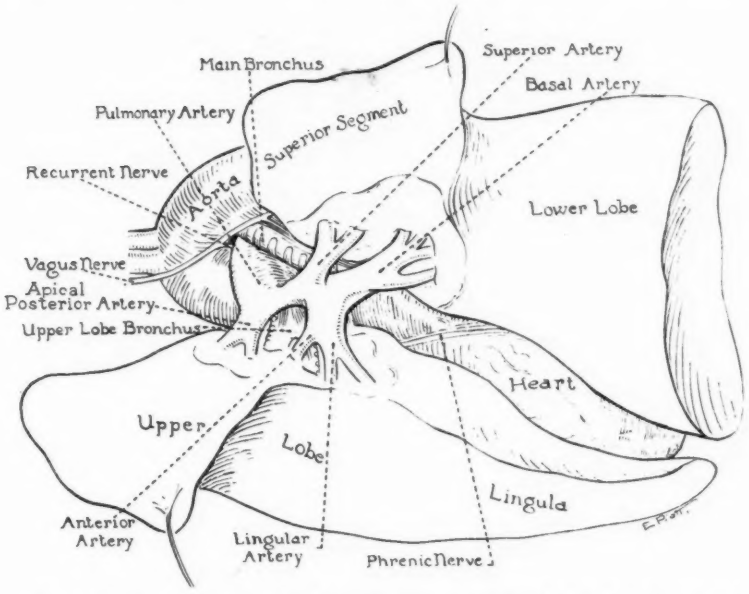

Fig. 2. Anatomical drawing of the left pulmonary artery with all of its branches as seen in the interlobar approach with both lobes retracted.

Not infrequently the presence of a rudimentary fissure, or crevice, will indicate the topographical boundary of a bronchopulmonary segment. Surface markings suggesting rudimentary fissures become more evident after the lung has been collapsed. The involved segments may be contracted or already completely collapsed. There may be a difference in pigmentation. The diseased segment sometimes fails to deflate as rapidly as the normal segments and variations in intrapulmonic pressure by inflating and deflating the lung will also aid in identification.

Accurate delineation of the bronchopulmonary segments is accomplished by: (1) deflation of the lobe, (2) temporary occlusion of the bronchus, (3) reinflation of the lobe by means of increased positive intratracheal pressure.

RELATED ANATOMY OF THE SEGMENTS

A thorough knowledge of the intrahilar and related segmental anatomy of the lung is indispensable if one is to apply the surgical principles of individual treatment of anatomical structures in partial lobectomy. The anatomical pattern may vary and an anomalous distribution of bronchovascular structures may be found. These anomalies can be recognized and do not interfere with the treatment of the segment as a surgical unit.

The pathological significance of certain segments selectively involved by bronchiectasis has already been referred to. The frequency in which bronchiectasis is found in both basal segments and in the lower division of the left upper makes these particular segments of great practical importance.[1]

Basal segments—right and left side. In normal lungs each basal group constitutes approximately two thirds of the lower lobe. In bronchiectasis this proportion changes as contraction of basal segments occurs and the superior segment hypertrophies or enlarges. In longstanding disease starting in childhood the superior segment has been found to approach in size the normal lower lobe. The hilar arrangements on both sides are similar.

[1]Related anatomy of only the most important segments involved in bronchiectasis has been given.

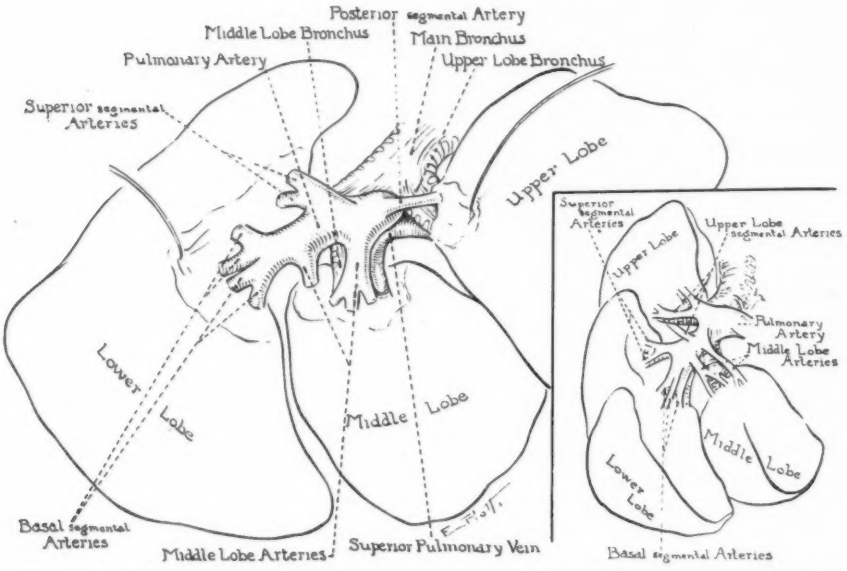

Fig. 3. Anatomical drawing of the right pulmonary artery and its branches as seen in the interlobar approach with the lobes retracted. Insert shows the pulmonary artery as seen anteriorly. The middle lobe has been retracted medially.

The inferior pulmonary vein is an anterior structure in the pulmonary root, but its tributaries emerge from the lobe in a plane posterior and inferior to the bronchus. Several tributaries from the lower lobes form the inferior pulmonary vein. They frequently are found to be four. One is from the superior segment, and the remaining three are from the basal segment. The branch from the superior segment lies posterior to the basal bronchus which it crosses and should be identified and preserved when basal segmental lobectomy is performed. This vein may be as large as the combined basal veins.

The bronchus to the lower lobe has two major segmental divisions: the superior and the basal. The first division of the lower lobe bronchus is the branch to the superior segment. It arises, both right and left, from the posterolateral aspect of the main bronchus. On the left side it arises below the level of the upper lobe bronchus and on the right side it arises at the beginning of the lower lobe bronchus about the level of the middle lobe bronchus. The bronchi in the basal segments are, in reality, the continuation of the main bronchi. Between the superior division of the bronchus and the subdivisions of the basal segmental bronchi there is a common stem from 1 to 1.5 centimeters in length which is suitable for individual ligation.

The arterial distribution of the lower lobes parallels, to a certain extent, the bronchial structures of it. The pulmonary artery on the left side (Fig. 2), during its course deep in the interlobar fissure, gives off branches to supply the segments. The highest artery to the lower lobe is the superior segmental branch. Its level or origin is opposite to the branch of the lingula and sometimes higher. On the right side (Fig. 3), this branch arises from the posterolateral aspect of the interlobar portion of the pulmonary artery opposite the level or slightly above the origin of the middle lobe artery or arteries. The basal segmental arteries (four on the right and three on the left) follow their respective bronchi. Their common stem which constitutes the prolongation of the main pulmonary artery is sometimes too short to allow its ligation in mass and for this reason each branch should be disposed of separately.

Fig. 4.

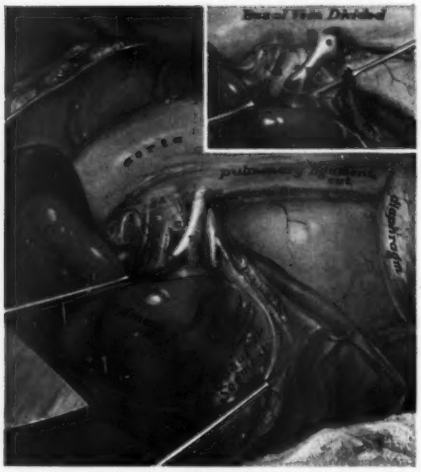

Fig. 5.

Fig. 6.

Fig. 7.

Lower division of the left upper lobe (lingula). The vein from the lingula division is a tributary to the superior pulmonary vein and enters it at its lowest point. It lies anterior and inferior to the bronchus and is formed by two branches: the superior, and the inferior, lingula veins. They are best approached from the anterior aspect of the hilum.

The lower, or lingula divisional bronchus, branches from the inferior aspect of the left upper lobe bronchus and its single trunk is divided into two segmental bronchi: the superior and the inferior. The inferior bronchus descends to the tongue of tissue in the anteroinferior angle of the upper lobe.

The artery to the lingula is a branch of the pulmonary artery, and it takes origin from the main trunk deep in the interlobar fissure (Fig. 2). Its course is posterior and lateral to the bronchus. Many variations in the lingula artery can be found. It may originate from a common trunk with the anterior segmental artery, or the two lingula branches may arise separately from the main pulmonary trunk.

TECHNICAL CONSIDERATIONS

Objection to clamp and suture method. In the past, segmental lobectomies or partial excision of pulmonary tissue have been accomplished by cutting through thick vascular pulmonary tissue between clamps and placing either a running suture ligature or individual ligatures in the lung substance held by the clamps. Distinct disadvantages of this practice should be mentioned.

1. It is impossible to place the clamps precisely in the intersegmental plane. Either too much or too little tissue is resected.

2. The application of clamps across the lung is rather crude and traumatizing. Bleeding and hematoma formation may be unavoidable.

3. Excessive suture material is necessary. This increases foreign-body reaction and predisposes to secondary infection.

4. Puckering and reduction in size of remaining segments are produced. Re-expansion may tear the sutured lung surface.

Our method. During the past year we have developed a method of segmental dissection which is fundamentally sound.

The segment is held within the lobe by four principal structures: the bronchus, the pulmonary artery, vein, and *visceral pleura.* All of these structures can be identified and divided prior to the dissection of the intersegmen-

Fig. 4. *1*, Left pulmonary artery; *2*, anterior artery; *3*, superior artery; *4*, lingula artery; *5*, basal artery; *B*, superior bronchus; *C*, basal bronchus. The fissure has been developed and the left upper and lower lobes are exposed. The basal segment is airless and appears contracted and dark bluish in color. The superior segment is larger than average and has normal color. The pulmonary artery is situated deep in the interlobar fissure. It is anterolateral to the bronchus. The basal artery is exposed and the superior lingula and anterior segmental arteries are seen through the visceral pleura which has been partially dissected away. The first step after exposure of the pulmonary artery is the ligature of the basal branch. If the common stem of this artery is short, the various branches can be ligated separately to provide more room between proximal and distal ties. The insert shows the basal artery already divided.

Fig. 5. *1*, Left pulmonary artery; *3*, superior artery; *A*, left main bronchus; *B*, superior bronchus; *C*, basal bronchus; *6*, inferior pulmonary vein; *7*, superior vein; *8*, basal vein. The lung has dropped forward exposing the posterior hilum. The pulmonary ligament has been divided. The inferior pulmonary vein lies anterior to the main bronchus, but its tributaries emerge from the lobe posterior to the segmental bronchi. Before the basal veins are ligated the superior segmental vein should be identified. It can be seen posterior to the basal bronchus and crossing over it. Insert shows the basal veins ligated.

Fig. 6. *A*, Left main bronchus; *B*, superior bronchus; *C*, basal bronchus; *6*, inferior pulmonary vein; *7*, superior vein. The insert shows the basal bronchus partially divided and the superior vein retracted. The main drawing shows the stump of the segmental bronchus closed. Tacking forceps hold the bronchus, vein, and artery of the segment. While the bronchus is being amputated the operative field should be protected with gauze pads in order to avoid spillage of purulent material. The suction tip is constantly maintained close to the amputation line. The lobe has been inflated by oxygen under pressure. The demarcation line between the segments is now evident. The visceral pleura at this boundary is incised. After the pleura is completely free, the dissection of the intersegmental plane begins in a retrograde manner.

Fig. 7. *A*, Left main bronchus; *B*, superior bronchus; *C*, basal bronchus; *6*, inferior pulmonary vein; *7*, superior vein. The insert shows finger method of separation. The surgeon's thumb is applied directly over the bronchi and all the branches are "peeled off." This simple procedure is very useful because the fingers find the path of least resistance which is the intersegmental plane. A few connective tissue fibers may have to be divided with a knife or scissors. In the main drawing, an intersegmental vein can be seen on the raw surface of the lobe. A few communicating vessels have been ligated. Air bubbles can be seen leaking out from the lung. They do not constitute a problem because the alveoli seal off spontaneously by the time the chest is ready to be closed. After the segmental lobectomy has been completed, all remaining bleeding points in the lung surface are sutured. If bronchial leaks are still present, they are repaired with interrupted sutures. Note the size of the remaining superior segment which represents a significant salvage.

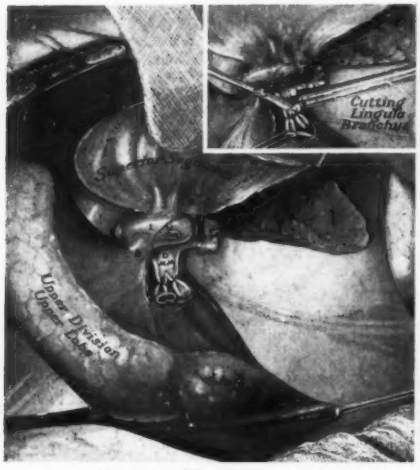

Fig. 8.

Fig. 9.

Fig. 8. *1*, Pulmonary artery; *2*, anterior artery; *3*, superior artery; *4*, lingula artery; *B*, superior bronchus; *D*, lingula bronchus. The remaining superior segment is retracted upward and the base of the fissure is exposed. The lingula artery has been prepared for ligation. Note that the lingula artery comes off from a slightly lower level than the artery to the superior segment. Both branches of the lingula artery have been tied distally and separately. The right angle clamp shown is used to dissect the artery. Proximally, the artery is going to be tied with a mass ligature of fine silk and a transfixion ligature. Insert shows the lingula artery divided. The lingula bronchus lies anteriorly to the artery. Its membranous portion can now be seen.

Fig. 9. *1*, Pulmonary artery; *D*, lingula bronchus; *9*, superior pulmonary vein; *10*, lingula vein. The upper lobe has been freed from the pericardium and is held up. The superior pulmonary vein is exposed. The tributaries from the upper lobe pulmonary segments can be seen. Superior and posterior to the superior pulmonary vein lies the main pulmonary artery. The mediastinal pleura has been opened and the lingula veins dissected. The ligatures are placed distally on the two branches. The cartilaginous portion of the lingula bronchus can be seen superior and posterior to the corresponding vein. Insert shows the lingula vein divided and the corresponding bronchus more clearly exposed.

tal plane; then the development of this plane is simplified and made possible. The bronchi do not traverse this plane. For practical purposes, this plane is avascular. The supporting framework of connective tissue is loose, slightly elastic, and yields to gentle, blunt, and sharp dissection. Air leak of raw surface is negligible and self-sealing. Prompt healing of the denuded lung surface follows, as in other organs, since its blood supply has not been jeopardized, or the tissue traumatized.

The technique as applied to any segment is briefly as follows:

1. Identify and divide the segmental pulmonary artery. In all segments except the apical posterior (left) and the apical and anterior (right), the major fissure should be developed in such a manner as to find the segmental artery.

2. Identify and divide the segmental vein.

3. Identify and divide the segmental bronchus.

4. Determine the line of demarcation between segments by inflation and incision of visceral pleura completely around the lobe at this line.

5. Start development of intersegmental plane at the secondary hilum. Holding forceps makes traction on the bronchus, artery, and veins. Clamps on the lung tissue are not used and should be avoided as they may include ramifications of the bronchi. Dissection is done bluntly at first. Fibrous strands may be cut with scissors. Bronchi strip out between forefinger and thumb. The correct plane of cleavage is the one showing least resistance. One to six intersegmental vessels may have to be ligated. Mosquito hemostats are used. If there is a question of identifying a fine bronchus or a vessel, it is first cut and then ligated

Fig. 10.

Fig. 11.

Fig. 10. *1*, Pulmonary artery; *2*, anterior artery; *3*, superior artery; *B*, superior bronchus; *D*, lingula bronchus. The bronchus to the lingula segment can be seen closed, proximally, with two mattress sutures. Both of its branches have been tied distally. Note the difference in the appearance of the lingula and the remaining portion of the upper lobe. Insert shows the bronchus being cut.

Fig. 11. *1*, Pulmonary artery; *2*, anterior artery; *C*, basal bronchus; *D*, lingula bronchus. Insert shows the free pleural flap held in place with an Allis forceps and sutured with two wire sutures. The main drawing shows the lobes re-expanded with oxygen under positive pressure. Note the size of the superior segment which has been conserved. The lingula segment is very small and contracted and the remaining segments in the upper lobe represent about 7/10 of that lobe. The lingula is in the process of being removed in the same fashion as the basal segment.

Fig. 12.

Fig. 13.

Fig. 12. Bilobar segmental bronchiectasis. Diseased segments, airless, contracted, and dark in color; as drawn from an actual kodachrome photograph.

Fig. 13. Healthy segments conserved after bisegmental resection; also from a photograph.

if it bleeds. If it happens to be a bronchus, the end is picked up again, and it is stripped out to its termination. Much of the dissection can be accomplished with the thumb and forefinger. It has been surprising to us to find that the structural attachment of the segment to the remaining portion of the lobe is so frail after the four supporting structures have been released. This completes segmental separation and treatment of the raw surfaces of the re-

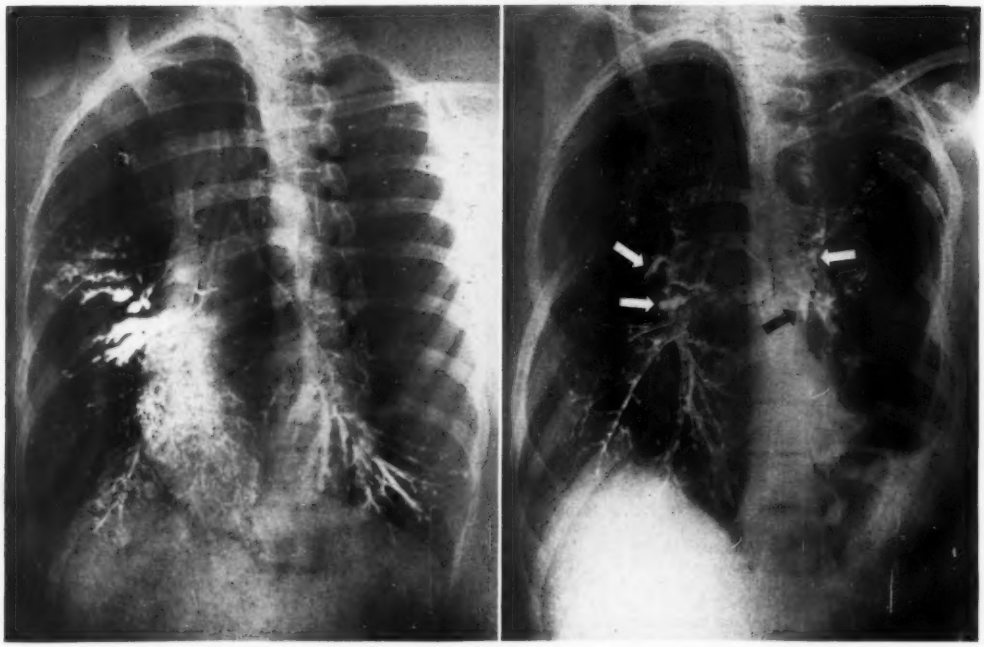

Fig. 14. Roentgenogram at left shows bronchiectasis in the middle lobe and anterior segment of the upper lobe on the right side and basal and lingula segments on the left side. Roentgenogram on right, 2 months after second operation. Arrows indicate stumps of resected segmental bronchi.

maining segment. No attempt is made to fold over edges or use grafts.

6. Reamputation and meticulous closure of the segmental bronchus is then carried out. We prefer to use two interrupted mattress sutures and two or three end sutures applied over a free graft of parietal pleura. Stainless steel wire (No. 35) or silk is used.

The resection technique of those segments most frequently removed for bronchiectasis is illustrated. The same principles may be applied to other segments (see Figs. 4 to 11). The patient is in the face-down position[1] and the head of the table is to the left. In all color drawings the artery is shown in red and the vein in blue.

[1]During the past year and one-half we have adopted the face-down position with the diseased side dependent for pulmonary resection (5). The conventional side position places the diseased lung above the healthy lung and favors spillage of secretions and débris via the intercommunicating bronchi during the operation. The face-down position minimizes this danger. It also permits a wider range of respiratory movement. Patients tolerate an open pneumothorax better and positive pressure is rarely required.

After completion of the operation the pleural cavity is thoroughly washed out with saline warmed to body temperature. The thoracic cage is reconstructed by two pericostal chromic catgut No. 2 sutures placed subperiostally. The intercostal nerves should be carefully avoided. Postoperative pain is greatly diminished by these precautions. The intercostal muscles are loosely sutured with interrupted sutures. The muscles are closed in two layers with interrupted sutures. The superficial fascia is closed separately and the skin is sutured with a multiple-needle technique. Silk (No. 9) is used throughout. Before the chest is closed a rubber catheter (No. 26) with lateral openings is placed in the pleural space and carried out through the lower end of the incision. Gentle suction is used for 24 to 48 hours.

POSTOPERATIVE ATTENTION

In the care of patients following segmental resection the same measures should be used

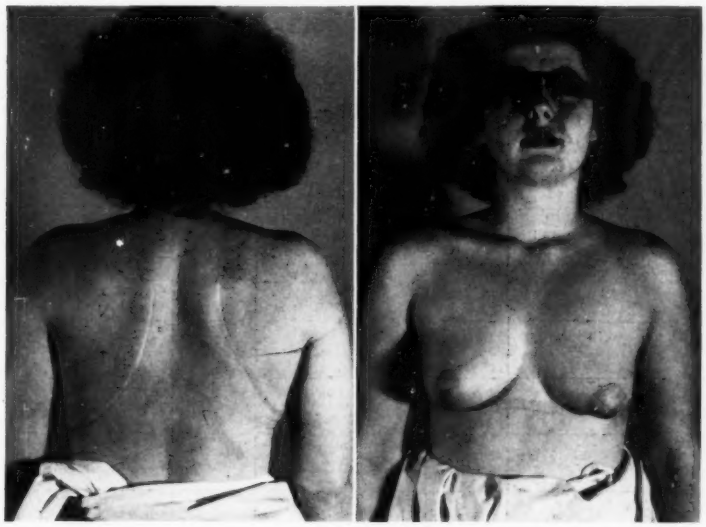

Fig. 15. Photograph of the patient, L. B. Front and back view 2 months following second operation.

that have been found to be of value after routine lobectomy. The two primary concerns are maintenance of airways and complete re-expansion of the remaining segments. Oxygen therapy is rarely needed. Deeper breathing is more apt to occur if the patients are in a normal atmosphere. Patients should be stimulated to cough and raise. Undue postoperative pain seriously interferes with expectoration. Early changes in position are encouraged. The lower half of the chest should be temporarily immobilized by exerting pressure with the hands on the side operated upon because it allows cough and expectoration with less discomfort. Bilateral bronchiectasis presents a particular problem after the operation on the first side because of the presence of secretions originating in the contralateral lung. Any accumulation of secretion should be avoided. Tracheal aspirations after insertion of a catheter via the nose will frequently suffice. The temporary catheter drainage is removed in 24 to 48 hours. Further evidence of fluid and air in the pleural cavity calls for aspiration by needle. Regular examination under the fluoroscope helps greatly in keeping track of the progress of re-expansion.

SUMMARY OF CASES

Twenty-three segmental resections have been performed upon 21 patients for primary bronchiectasis. No deaths have occurred in this series, and all of the patients have benefited greatly from the surgical intervention. All of the unilateral cases are free of symptoms. The age of the patients ranged from 7 to 56 years. Most of the patients were in the second or third decades. The duration of the disease was from 4 months to 27 years. The amount of sputum varied from 1 ounce to 20 ounces daily. The outstanding clinical features in the order of severity were as follows: repeated colds, bouts of pneumonitis, hemoptysis, cough, and expectoration of purulent secretions. Foul sputum was present in 40 per cent of the cases. Bilateral lesions were present in 11 cases (52.4 per cent) with the following segmental distributions: In 10 cases the middle lobe, right basal, and lingula and left basal segments were involved; 1 patient had the middle lobe, the anterior segment of the right upper, and the lingula and left basal diseased. In the unilateral group 5 patients showed involvement of two segments. The lingula and left basal were involved in 3 cases, and the

TABLE I.—SUMMARY OF 21 CASES (23 OPERATIONS) AS TO AGE, DURATION OF DISEASE, AMOUNT OF EXPECTORATION, SEGMENTS INVOLVED, SEGMENTS REMOVED, POSTOPERATIVE COMPLICATIONS, AND PRESENT CLINICAL STATUS.

Case No. Name Age	Duration of illness	Segments involved	Amount of sputum (ounces)	Segments removed	Date of operation	Complications	Present clinical status
1 L.B. 19	15 yrs.	Middle lobe, anterior segment, upper lobe, lingula and basal left	5 ozs.	Middle lobe and anterior segment, upper lobe, lingula and basal left	3-14-45 12-10-45	Atelectasis 15th P. O. day	Well
2 M.M. 7	2 yrs.	Middle lobe and basal right lingula and basal left	3 ozs.	Middle and basal right lobes, lingula, and basal left	4-17-45 8-22-45	—	Well
3 R.D. 42	27 yrs.	Middle lobe and basal right lingula and basal left	8 ozs.	Lingula and basal left	7-10-45	Fistula and empyema Drained 22nd P. O. day	Cough and expectoration 1 ounce Draining very little
4 E.D. 13	10 yrs.	Lingula and basal left	3 ozs.	Lingula and basal left	8-28-45	Atelectasis 1st P. O. day	Well
5 M.M. 35	20 yrs.	Basal left	2 ozs.	Basal segment	9-5-45	—	Well
6 M.R. 17	4 mos.	Basal right	1½ ozs.	Basal segment	9-7-45	—	Well
7 B.B. 17	5 yrs.	Lingula and basal left	2 ozs.	Lingula and basal left	9-4-45	Atelectasis 2nd P. O. day	Well
8 J.H. 19	9 yrs.	Middle lobe and right basal lingula and basal left	4 ozs.	Lingula and basal left	9-19-45	—	Still raises a slight amount of thick sputum
9 F.J. 18	4 yrs.	Middle and right basal, lingula and basal left	4 ozs.	Lingula and basal left	9-19-45	Empyema—cured with penicillin	Well
10 C.S. 18	1 yr.	Lingula and basal left	2 ozs.	Lingula and basal left	10-24-45	—	Well
11 M.B. 13	7 yrs.	Lingula and basal left middle lobe and basal right	2 ozs.	Lingula and basal left	12-12-45	Atelectasis, bronchopleural fistula and empyema—drained 12th P. O. day	Still draining very little Fistula closed Slight expectoration
12 A.M. 18	4 yrs.	Basal right	2 ozs.	Basal right	11-30-45	—	Well
13 I.W. 18	1 yr.	Middle lobe and right basal lingula and basal left	4 ozs.	Lingula and basal left	1-13-46	Empyema drained 33rd P. O. day	Still draining very little. No sputum
14 N.R. 20	5 yrs.	Middle lobe and basal right lingula and basal left	10 ozs.	Lingula and basal left	2-15-46	Bronchopleural fistula repaired	Raises about 2 ounces of sputum
15 J.G. 56	15 yrs.	Middle lobe and basal right lingula and basal left	5 ozs.	Lingula and basal left	3- 7-46	—	Well
16 W.McG. 28	5 yrs.	Superior segment left	1 oz.	Superior segment left	3-20-46	—	Well
17 V.S. 30	3 yrs.	Middle and right basal lingula and left basal	2 ozs.	Middle lobe and right basal	4- 9-46	—	Raises a teaspoonful of mucoid sputum
18 R.McD. 39	5 yrs.	Middle and right basal	3 ozs.	Middle and right basal	4-15-46	—	Well
19 R.H. 15	9 yrs.	Basal left	½ oz.	Basal left	5-25-46	—	Well
20 M.F. 23	7 yrs.	Lingula middle and right basal	1 oz.	Lingulectomy	6-22-46	—	Too recent to evaluate
21 J.M. 11	6 yrs.	Middle and right basal lingula and left basal	4 ozs.	Lingula and left basal	6-24-46	—	Too recent to evaluate

middle lobe and right basal segment were involved in the other 2 patients. The remaining 5 patients had their disease localized to only one segment, as follows: Two were in the right basal, 2 in the left basal; 1 had the superior segment of the left lower lobe involved.

Bilateral bisegmental operations were performed in 2 cases, 1 in a 7 year old girl. During the first stage the middle and right basal segments were removed. Four months later the lingula and left basal segments were resected. The other patient was a 19 year old female who had a history of 15 years of cough and purulent sputum. During the first operation the middle and the anterior segment of the right upper were resected. Nine months later the lingula and left basal segments were operated upon. Both patients made an uneventful recovery following the operation and are free of symptoms.

COMPLICATIONS

In 4 cases bronchoscopy was necessary to aid in re-expansion. In each instance watery secretions were found but no definite bronchial plug. Bronchoscopy also revealed submucosal edema of the orifice of the segment adjacent to the amputated one. We believe that this pathological finding explains the obstructive atelectasis in the absence of a bronchial plug. In times past, when all diseased segments were not removed, thick, tenacious sputum was a frequent postoperative finding. Following bronchoscopy, all of the patients' conditions improved and re-expansion was obtained. Empyema developed in 4 cases. One was treated locally with pleural aspiration and penicillin and cleared up entirely. The remaining 3 were drained. Bronchopleural fistula was demonstrated in 2. In 1 of them a tension pneumothorax developed requiring an exploratory thoracotomy. This was performed 20 days after the segmental resection and revealed a pinpoint opening in the basal bronchial stump. This defect was repaired with interrupted sutures. Continuous negative suction was applied and re-expansion was obtained.

The incidence of complications in this series of segmental resections is greater than that which attended routine lobectomy, for the incidence of empyema has been brought down to approximately 5 per cent. This segmental series, however, is an original group and there is reason to believe that a reduction in complications will follow. It should be pointed out that at the present time the conservation of uninvolved pulmonary tissue far offsets any effects of a temporary pleural infection which may occur. Functional studies have not been done in this group of cases. In the future, when these studies can be undertaken, we are confident that comparative studies will reemphasize the importance of selective segmental resection for bronchiectasis.

CASE REPORT

L. B., student nurse, 19 years of age. Patient had a chronic cough dating as long as she could remember. Recently the cough was productive of thick, yellowish sputum daily. She had been having frequent colds, episodes of pneumonitis, and dyspnea. She was forced to give up work. Bronchographic studies (Fig. 14, a) revealed cylindrical bronchiectasis in the middle lobe and anterior segment of right upper lobe and in the lingula and basal segments of the left lower lobe. On March 14, 1945, a middle lobectomy and resection of the anterior segment of the right upper lobe was performed. On December 10, 1945, the lingula and basal segments on the left were removed. Bronchogram (Fig. 14, b) taken 2 months after second operation showed the remaining segments to be well re-expanded and free of bronchiectatic changes. The four segmental stumps can be seen. The superior segment of the left lower lobe now occupies the lower lung field.

CONCLUSIONS

1. A new method of removing a pulmonary segment, applicable to any segment, has been described. This method does away with the use of clamps or suture of the lung surface. The development of the intersegmental plane is precise, relatively avascular, and not traumatizing.

2. The importance of considering the bronchopulmonary segment as a surgical unit in the management of bronchiectasis has been discussed. The frequency of bilateral and multiple segmental involvement has been pointed out.

3. Conservation of all healthy pulmonary tissue is desirable in all cases and obligatory in bilateral disease. It is vitally important that the surgeon limit the resection to diseased seg-

ments rather than remove entire lobes, segments of which are healthy and capable of respiratory function.

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CLINICAL EXPERIENCES WITH THE USE OF PENICILLIN TREATMENT OF INFECTIONS INVOLVING BONES AND JOINTS

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A CLINICAL investigation of the efficacy of penicillin in the treatment of infections involving the bones was begun on the University of California surgical services in April, 1944, and continued until March, 1945, after which the study was limited to bone grafting in infected areas and to the treatment of infections of the central nervous system and skull. During this period, 87 patients with infections involving the bones and joints were studied. There were 58 cases with established infections of the large bones and joints (20 acute and 38 chronic), 4 cases with infections of the mandible, and 25 cases with infections involving the bones of the skull (the latter, with infections of the central nervous system, will be reported elsewhere). Frequent bacterial cultures, blood penicillin levels and penicillin sensitivity tests accompanied the study of all cases (Table I).

ACUTE INFECTIONS INVOLVING BONES AND JOINTS

There were 20 patients with acute infections involving the large bones and joints; 7 had postoperative infections, in 4 infections followed injuries, and 9 had acute hematogenous osteomyelitis.

1. *The acute hematogenous infections* included 7 cases of acute osteomyelitis (2 tibias, 1 femur, 1 clavicle, 1 clavicle and sternum, 1 humerus, and 1 ilium) and 2 cases of acute septic arthritis (knee and hip joints). Five of the 9 patients had fulminating infections of 1 to 5 days' duration, with temperatures of 104 to 105 degrees F., and with blood cultures positive for hemolytic Staphylococcus aureus in 4 cases and beta hemolytic streptococcus, 1 case. The other 4 patients had been acutely ill for 2 to 8 weeks, with temperatures 101 to 103 degrees F., with hemolytic Staphylococcus aureus infections, but their blood cultures were sterile. The organisms were penicillin-susceptible in all cases. In 5 cases a period of sulfonamide therapy given prior to penicillin treatment had failed to control the infection. Systemic penicillin was given by the intramuscular route at 3 hour intervals in all cases.

The initial dosage varied from 100,000 to 200,000 units per day. This was increased to 200,000 or 300,000 units per day within 24 to 48 hours if response to treatment appeared slow. The patients with fulminating infections usually became less toxic and the blood cultures became sterile within 48 to 72 hours after systemic penicillin therapy was started, but the temperatures declined rather slowly over a period of several days. The patients with less severe infections showed more rapid diminution of temperature and toxicity. The small abscesses and all infected joints were aspirated and penicillin solution was instilled into them. Usually concentrations of 5,000 units of penicillin per cubic centimeter were used in the abscesses and 1,000 units per cubic centimeter in joints. Infected joints and small abscesses usually became sterile after 48 hours of local penicillin therapy, but aspirations and instillations were continued as long as fluid could be obtained. Large abscesses necessitated surgical incision for drainage in 4 of the 9 cases. Two of these were in the group of 5 patients with the fulminating infections, and 2 were in the group of 4 patients with less severe infections. Transfusions of blood were required in only 2 cases. All patients were kept in bed during the height of the infection and

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TABLE I.—BACTERIAL CULTURES FROM PATIENTS WITH BONE INFECTIONS

Organisms	Acute hematogenous osteomyelitis	Chronic hematogenous osteomyelitis	Infected fractures	Other injury to bone with infection	Postoperative bone infection—acute	Postoperative bone infection—chronic	Infections of the mandible	Tuberculosis of the bone with secondary infection
Hemolytic Staphylococcus aureus	8	3	7	1	4	2	2	2
Beta hemolytic streptococcus	1			1			1	
Beta hemolytic streptococcus and hemolytic Staphylococcus aureus			2	1	2	1		
Hemolytic Staphylococcus aureus and Escherichia coli		1	1		1			
Hemolytic Staphylococcus aureus and alpha hemolytic streptococcus		1	1	1				
Anaerobic staphylococcus, streptococcus, actinomyces and bacteroides							1	
Nonhemolytic Staphylococcus aureus		1	2					
Hemolytic and nonhemolytic Staphylococcus aureus		1						
Hemolytic Staphylococcus aureus and Aerobacter aerogenes		1						
Hemolytic Staphylococcus aureus and hemolytic Staphylococcus albus		1				1		
Hemolytic Staphylococcus aureus, beta hemolytic Streptococcus and Proteus vulgaris		1						
Hemolytic and nonhemolytic Staphylococcus albus		2						
Nonhemolytic Staphylococcus aureus, Streptococcus fecalis and Clostridium welchii			1					
Hemolytic Staphylococcus aureus and Bacillus pyocyaneus			1					
Hemolytic Staphylococcus albus			1					1
Beta hemolytic streptococcus, Streptococcus fecalis and staphylococcus			1					
Gamma streptococcus and nonhemolytic staphylococcus			1					
Hemolytic and nonhemolytic Staphylococcus aureus, gamma Streptococcus and anaerobic nonhemolytic streptococcus						1		

plaster-of-paris cast immobilization was applied in 4 cases. The duration of systemic penicillin therapy varied from 31 to 75 days, averaging 51 days. The total amount of penicillin used for systemic treatment in each case varied from 1,100,000 to 8,550,000 units and averaged 5,403,500 units per case.

The results in 8 of the 9 cases of acute hematogenous infections involving bones and joints were excellent. All 8 healed and remained healed with good functional use of the affected bone, except in one patient who developed a draining sinus 4 months after he was discharged from the hospital and was readmitted for further treatment. One other patient developed slight soft tissue swelling at the original site of infection 1 year later, but no suppuration occurred. In 2 cases large pieces of infected bone that had appeared by x-ray as sequestra, became revascularized and incorporated into the repair of the bone under penicillin therapy. In the patients in whom penicillin therapy was begun very early, x-ray evidence of osteomyelitis often did not appear until several weeks or months after all clinical evidence of infection had disappeared, and these x-ray changes in the bone appeared to be very small in extent, considering the severity of the original acute infection.

One of the 9 patients in this group of acute hematogenous infections had an acute monocytic leucemia in addition to a carbuncle of the chin and an abscess of the hip involving the ilium. It was interesting to observe that in

spite of the fact that the organism (hemolytic Staphylococcus aureus) was quite susceptible to penicillin, the cultures obtained from the wound (drained surgically) grew the organism on all occasions; and the patient showed no evidence of favorable response either clinically or bacteriologically to penicillin treatment of his infection. This patient died with his leucemia and the infection, and this was the only death that occurred in this group of acute hematogenous infections.

2. The 7 cases of established *acute postoperative infections* involving bones included 1 spinal fusion with cancellous bone grafts, 1 acetabuloplasty, 1 triple arthrodesis, 1 thigh amputation, 1 Smith-Peterson nailing of a fractured neck of the femur, 1 open operation on the tibia and 1 on the sternum. The temperatures at the time of beginning treatment varied from 101 to 104 degrees F. The bacterial cultures were beta hemolytic streptococcus, hemolytic Staphylococcus aureus (in 2 cases both were present) and Escherichia coli (in combination with hemolytic Staphylococcus aureus). The Escherichia coli was not susceptible to penicillin, and one of the strains of hemolytic Staphylococcus aureus was penicillin-resistant. Systemic penicillin therapy was given by the intramuscular method at 3 hour intervals in all cases within a day after the infection was discovered. Individual dosage varied from 100,000 to 300,000 units per day. The duration of treatment varied from 11 to 112 days and averaged 39 days. The total amount of penicillin used varied from 1,300,000 units to 11,200,000 units, averaging 4,813,000 units. The wounds were opened for drainage in 5 of the 7 cases, and left closed in 2 cases. In 4 of the wounds that were opened, pus and débris were thoroughly cleaned out, small rubber catheters were placed in the depths of the wounds, and the wounds immediately closed. Postoperatively, penicillin was instilled by continuous drip in 1 case and by instillations given once daily in 3 cases. In 1 case in which the organisms were Escherichia coli and hemolytic Staphylococcus aureus, the Escherichia coli persisted, and an additional contaminant, Bacillus pyocyaneus, was inadvertently introduced and resulted in prolonged profuse suppuration of the wound. In 1 of the cases in which there was a hemolytic Staphylococcus aureus that was relatively resistant to penicillin, systemic penicillin failed to control it, but the concentrations obtained with local penicillin rapidly sterilized the infection. Three patients required transfusions of blood.

The results of penicillin therapy in this group of acute postoperative infections involving bone were excellent. In the case in which there was penicillin-resistant Escherichia coli and contamination with Bacillus pyocyaneus, these organisms produced only a prolonged suppuration of the soft tissues overlying bone, which temporarily delayed healing.

3. Four patients had acute *infections of bone and joints associated with injuries*. Two were old gunshot wounds involving the humerus and hip joint, with recent acute exacerbations of infection, resulting in abscesses, one was an acute penetrating injury to the knee joint, and the other infection resulted from a steel fragment entering the thumb. The organisms were beta hemolytic Streptococcus, hemolytic Staphylococcus aureus (combined in 1 case), and alpha hemolytic streptococcus (with hemolytic Staphylococcus aureus). All organisms were penicillin-susceptible except the alpha hemolytic streptococcus, which was relatively resistant to penicillin. Three of the patients had systemic penicillin therapy for 7 days, 17 days, and 32 days, respectively, with dosages of 100,000 to 200,000 units daily. Two of these had surgical incision for drainage, but no local penicillin was used. The patient with acute purulent arthritis of the knee joint had the penicillin-resistant alpha hemolytic streptococcus and hemolytic Staphylococcus aureus, and this infection was not controlled until the systemic penicillin therapy and aspirations were supplemented with 50,000 units of penicillin instilled daily into the joint, after which the joint fluid became sterile in 48 hours, and recovery began. Local penicillin instillations were given for 6 days in this case. One patient had a large abscess involving an old gunshot injury of the humerus, which was drained surgically and then treated with local instillations of 1,500 units of penicillin twice daily for 7 days; no systemic penicillin was used in this case. The results in all 4 of these cases were excellent.

INFECTIONS OF THE MANDIBLE

Four patients with serious infections involving the mandible were treated with penicillin. Two had chronic infections with penicillin-susceptible hemolytic Staphylococcus aureus. One of these had an extensive chronic osteomyelitis and the other an infected fracture of the mandible with nonunion. Two patients had acute infections of the mandible; one had an acute osteomyelitis arising from a carious tooth with a large abscess involving bone and soft tissues and containing anaerobic staphylococcus, streptococcus, actinomyces and bacteroides; the other an osteomyelitis, apparently from a carious tooth, resulting in a fulminating bacteriemia with beta hemolytic streptococcus.

The first patient had an operation for drainage and removal of sequestra, and received 1,800,000 units of systemic penicillin therapy over a period of 18 days. The wound was left open and healed promptly with an excellent result. The patient with an infected fracture had an open reduction, including a sliding bone graft, done in conjunction with 3,700,000 units of penicillin given systemically over a period of 23 days. The wound healed without infection; the bone graft was successful and gave a satisfactory functional result.

Two patients had acute infections involving the mandible. Both apparently originated from infected teeth. One had a large abscess containing anaerobic streptococcus, staphylococcus, actinomyces, and bacteroides. It was aspirated daily for 6 days, and 50,000 units of penicillin were injected daily for the first 3 days and 25,000 units on each of three other occasions. Cultures became sterile 72 hours after therapy was started. The patient recovered rapidly and completely, and subsequently the offending tooth was extracted without complication. The remaining patient had a fulminating bacteriemia with beta hemolytic streptococcus that apparently originated in the infected mandible. This patient was unconscious and had general anasarca when treatment was begun. She was treated for 3 days with 300,000 units of penicillin per day and transfusions of blood, but these measures were not successful and the patient expired.

CHRONIC INFECTIONS OF BONES AND JOINTS

In this group of 38 patients there were 12 with chronic infections resulting from hematogenous osteomyelitis, 18 with infected fractures, 5 with postoperative infections of the bone in a chronic phase, and 3 patients with tuberculosis of the bones, associated with chronic secondary pyogenic infections. Systemic penicillin therapy was given by the intramuscular route at 3 hour intervals. The improvement in appetite and nutrition of this group of patients within a few days after beginning systemic treatment with penicillin was striking. The drainage from the infected sinus tracts often became clear or opalescent, and in a few cases ceased entirely after a few days of penicillin therapy.

1. The *chronic bone infections* resulting from hematogenous osteomyelitis included 2 cases of osteomyelitis of the humerus, 2 of the tibia and 8 of the femur, in 1 of which the hip joint was involved. The bacterial flora in these patients were: hemolytic and nonhemolytic Staphylococcus aureus (occuring alone and together), hemolytic and nonhemolytic Staphylococcus (combined), and mixtures of hemolytic Staphylococcus aureus with Escherichia coli, Aerobacter aerogenes, hemolytic Staphylococcus albus, alpha hemolytic streptococcus, beta hemolytic streptococcus and Proteus vulgaris. The organisms were penicillin-susceptible except the Escherichia coli, Proteus vulgaris, Aerobacter aerogenes, which were very resistant, and the alpha hemolytic streptococcus which was very slightly susceptible to concentrations of penicillin obtainable in the blood stream.

Two patients with chronic osteomyelitis, 1 of the humerus and 1 of the femur, were treated with systemic penicillin without operation. One received 1,700,000 units over a period of 17 days and the other received 6,000,000 units over a period of 71 days. The infected sinuses ceased to drain on the 11th and 17th days after treatment was begun, and both patients remained completely healed for periods of about 1 year, when their osteomyelitis again became active and the draining sinuses recurred.

The 10 other chronic osteomyelitis patients had operations in conjunction with systemic

penicillin therapy. All 10 of these patients had a course of preoperative penicillin therapy of 3 to 15 days' duration, averaging 8 days. The preoperative penicillin dosage varied from 100,000 to 200,000 units per day. Postoperatively systemic penicillin was continued for not less than 3 weeks and usually at least 6 to 8 weeks. The total amounts of systemic penicillin used in treatment in each case varied between 1,900,000 and 17,800,000 units, averaging 4,499,000 units. The operations consisted of excision of all infected scars, granulations, sinus tracts, and sequestra, and excision of infected bone as far as was practical. The soft tissue wounds were closed at once in 6 of the 10 cases and 4 of these healed promptly without infection; one wound disrupted on the 5th postoperative day, but subsequently healed slowly and satisfactorily, and the other wound became grossly infected (hemolytic Staphylococcus aureus and Aerobacter aerogenes) on the 7th postoperative day, but subsequently healed and has remained healed. Three of the patients had secondary closures performed on the 14th, 16th, and 17th postoperative days, and all of these soft tissue wounds healed promptly and remained healed. The wound of 1 patient was left open and healed slowly, but completely, by granulation. Four patients (2 with primary closures and 2 with secondary closures) had local penicillin therapy given postoperatively through rubber tubes that were placed in the wounds at the time of operation, and healing was rapid and complete in all 4 patients.

At the time this report was prepared there was no sign of activity of osteomyelitis in any of the 10 patients treated with operation in conjunction with penicillin therapy, and the soft tissue wounds in all were completely healed. The 2 patients who were treated with penicillin therapy alone had excellent temporary results, but both had a recurrence of infection after having remained healed for a year.

2. *Chronically infected fractures.* In the group of 18 patients with chronically infected fractures, the tibia was involved in 13 cases, the femur in 3 cases, and the humerus in 2 cases, 1 including the elbow joint. The organisms cultured from the wounds of these patients were: hemolytic Staphylococcus aureus (occurring alone and with Bacillus pyocyaneus, Escherichia coli, beta hemolytic streptococcus and alpha hemolytic streptococcus), nonhemolytic Staphylococcus aureus (separately and mixed with Streptococcus fecalis plus Clostridium welchii, and with gamma streptococcus), hemolytic Staphylococcus albus and a mixture of beta hemolytic streptococcus, Streptococcus fecalis and staphylococcus.

All of these patients required operation. They usually received a few days of preoperative penicillin therapy, and in 3 cases several weeks of penicillin therapy preceded operations on infected fractures. Operation usually consisted of excision of infected scar, sinuses and granulations, and removal of infected and nonviable bone, so that only well vascularized soft tissues and bone remained. At the same time, open reduction of the fractures was performed. In 6 of these patients internal fixation with large metal plates was used, and bone grafting was done in 13 of the patients. Position of the fragments was maintained with appropriate orthopedic methods of fixation. Multiple operations were required in some cases; 4 patients had 2 operations, 4 patients had 4 operations and 1 patient had 5 operations. The additional procedures consisted of skin grafting, secondary closures, removal of metal plates and regrafting fractured bone grafts. Each operation was done in conjunction with a preoperative and postoperative course of penicillin therapy. There was no indication of dissemination of infection following any of the surgical procedures. The wounds were closed by primary suture in 16 of the 18 cases. Eight of these healed *per primam,* 3 had some necrosis of the soft tissue wounds due to closure under tension, 2 developed trivial superficial infections, and 3 wounds broke down with gross infection. The wounds of two of the 18 patients were left open, and a trivial infection developed in 1 of these.

All patients received their systemic penicillin by intramuscular injection at 3 hour intervals. The daily dosage usually was 100,000 to 200,000 units. The total amounts of penicillin used in each case varied from 1,800,000 to 20,000,000 units, averaging 7,600,000 units

per patient. An effort was made to maintain systemic penicillin therapy until all of the contaminated fracture area and overlying soft parts were vascularized completely, and until bony repair was well begun. In some cases in which tension necrosis or superficial infection produced open wounds, local bacteriostasis was maintained with penicillin ointment dressings. Four of the patients had postoperative local instillations of penicillin solution through catheters placed in the wounds at operation; in 3 of these, healing was prompt and complete; in one the introduction of pyocyaneus delayed healing of the soft tissues, but the final result was good. These tubes for local penicillin therapy were removed between the 10th and 14th postoperative days. Apparently firm union occurred at the fracture site in 13 of the 18 cases, 1 patient has fibrous union with poor function and 4 patients still have nonunion. At present the soft tissue wounds of 13 patients are completely closed, 2 have small superficial granulating areas and 3 have open infected draining wounds.

3. *Chronic postoperative bone infections.* Five patients had chronic infections of the bones resulting from previous operations. These included patients with the following conditions: an infected osteotomy of the tibia (poliomyelitis deformity), an infected revision of an amputation stump in the lower leg, an infected spinal fusion (performed for a fracture of the odontoid process), an infected hip joint arthrodesis (performed for traumatic arthritis), and an infection involving bones of the pelvis following an attempted lumbosacral fusion operation. The predominating organism found in this group was hemolytic Staphylococcus aureus, which occurred alone and with hemolytic Staphylococcus albus, beta hemolytic streptococcus, and in 1 case was mixed with nonhemolytic Staphylococcus aureus, gamma streptococcus and anaerobic nonhemolytic streptococcus. All organisms were penicillin-susceptible *in vitro*. Each patient received a course of systemic penicillin consisting of 100,000 units daily for 3 to 11 days (average 8 days). In this group all 5 patients had operations for removal of infected and nonviable bone, scar, granulations, and sinuses. The wounds of all patients were closed by primary suture without drainage. Tubes were placed for postoperative local penicillin therapy in 2 cases. Postoperative systemic penicillin therapy was maintained for 14, 20, 43, 68, and 137 days, respectively, and the total penicillin dosage in these 5 cases was 1,400,000 units, 2,000,000 units, 4,299,000 units, 5,150,000 units, and 16,500,000 units.

The soft tissue wounds healed without infection in 3 of the 5 patients. In 2 patients Proteus vulgaris infections occurred postoperatively and produced serious acute infections followed by prolonged suppuration of the soft tissues, but after several weeks both of these wounds healed completely. (One of the proteus infections occurred in a patient receiving local penicillin therapy through a rubber catheter; the other occurred in a patient who did not receive local penicillin therapy.) Subsequently these 5 patients have exhibited excellent results, all wounds remaining healed.

4. *Tuberculosis of the bone and joints with secondary pyogenic infection.* The 3 patients in this group were treated with penicillin. One patient had tuberculosis of the spine (sixth thoracic to second lumbar) with multiple sinus tracts and secondary infection with a penicillin-sensitive strain of hemolytic Staphylococcus aureus. He was given three separate courses of systemic penicillin therapy consisting of 100,000 units per day for 18 days, 14 days, and 37 days, respectively. The secondary infection (hemolytic Staphylococcus aureus) responded slowly, but apparently was controlled temporarily by penicillin therapy. However, infection with the same organism recurred within a few weeks after each course of penicillin treatment. He received a total of 7,380,000 units of penicillin.

The second patient had tuberculosis involving the bones about the shoulder joint. The secondary infection in this case was a penicillin-resistant hemolytic Staphylococcus albus. He received 2,100,000 units of systemic penicillin therapy over a period of 22 days without benefit. Suppuration from the draining sinuses was unchanged and the bacterial cultures remained positive for hemolytic Staphylococcus albus.

The third patient had long-standing chronic tuberculosis of the knee joint, with extensive

osteomyelitis of the femur and tibia. Cultures of the wounds grew a strain of hemolytic Staphylococcus aureus that was penicillin-susceptible. Systemic penicillin was given preoperatively for 7 days (150,000 units per day). At operation the sinus tracts, granulations, sequestra, and infected bone were excised thoroughly. Cancellous bone grafts from the ilium were placed in the large resulting defect, a tube was placed for postoperative local penicillin therapy, the wound was closed without drainage, and the extremity was fixed with steel pins in a plaster-of-paris cast. Postoperative local penicillin therapy consisted of 10,000 units per day for 10 days, after which the tube was removed. Systemic penicillin therapy was maintained for 46 days. A total of 6,750,000 units of penicillin was given to this patient. The wound healed *per primam*. The bone grafts became vascularized and incorporated in a repair that produced complete arthrodesis. One year later this patient was seen to have excellent function of the extremity.

Systemic penicillin therapy proved to be a valuable adjunct to the surgical treatment of chronic infections involving bones. Complete surgical removal of all infected tissues and nonviable bone appears to be of primary importance in the successful penicillin treatment of most patients with chronic bone infections. Incomplete surgical removal of infected tissues is the most important cause for failure with penicillin therapy. In some cases it was impossible to remove all of the infected sclerosed bone, e.g. in a patient with osteomyelitis involving an entire long bone or large segment of the spine, and in such cases recurrence of infection is inevitable. Internal fixation with metal plates almost invariably produced complications in the form of necrosis of the overlying soft tissues or delayed recurrence of the bone infection, and it appears desirable that such plates, when indispensable, be removed at the earliest suitable time. Tension of the overlying soft tissues consistently resulted in necrosis and infection with penicillin-resistant organisms. Bone infections associated with very large, open soft tissue defects were difficult to control because of reinfection through the open wound. Bone grafting in contaminated and infected areas was accomplished successfully in conjunction with penicillin treatment, and several bone grafts in wounds that became infected postoperatively were saved by administration of penicillin.

Preoperative systemic penicillin for a period of several days appeared to be desirable, and postoperatively it was found necessary to maintain systemic penicillin therapy until the soft tissues were healed and the bone defects were revascularized and had started their repair. This generally required at least 3 weeks and often several months, depending on the size of the soft tissue and bony areas to be revascularized and on the vascularity of the tissues adjacent to the site of healing. Doses of 100,000 to 200,000 units daily were used, but in most serious chronic infections it appears desirable to give at least 200,000 units per day. Inadequate dosage, i.e., small doses, doses given infrequently or adequate doses given for too brief periods, is ineffective. Whenever the infected area was accessible to local penicillin therapy, the control of infection and healing seemed to take place more rapidly than with systemic penicillin therapy alone. Local penicillin treatment was particularly useful in controlling infection in large defects, and in areas contaminated with organisms that were somewhat resistant to penicillin levels obtainable in the blood, but susceptible to higher concentrations of penicillin. It proved to be desirable to remove the tubes used for local therapy by the 14th postoperative day and it was necessary to avoid contamination with penicillin-resistant organisms. Such contamination usually produces only prolonged suppuration of soft tissues, but will permit reinfection of the bone unless penicillin therapy is maintained until healing takes place.

CARCINOMA OF THE PROSTATE

Review of 130 Cases Treated between 1940 and 1946

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PHYSICIANS who deal with carcinoma of the prostate are appalled at the consistently fatal outcome of this disease. In addition, it carries a high operative mortality (approximately 20 per cent for radical removal and in our hands 11 per cent for lesser operative interventions). Careful rectal palpation may provide an early diagnosis; however, when carcinoma is occult and when it originates in the median or lateral lobes, this method fails. The hard nodule, which is usually situated in the posterior lobe, can be confused with localized inflammatory lesions and calculi. It is only at this stage that radical perineal prostatectomy can be carried out with any hope of cure, and even then the disease may already have extended beyond the prostate via the lymphatics. The great majority of patients consult the urologist after cancer has extended well beyond the confines of the prostatic capsule, often associated with extensive metastases, uremia, and cachexia. These cases present the immediate problem of affording relief of urinary obstruction and ameliorating toxic symptoms of the disease, thereby prolonging life.

Radical perineal prostatectomy is the method of choice for treatment of early carcinoma of the prostate. In advanced cases, until recently the obstructing portion of the gland was removed suprapubically or perineally. These procedures have been gradually supplanted by transurethral resection, as it provides a satisfactory channel and is a far more benign intervention. Two to three decades ago, operative relief of obstruction was supplemented by radiation therapy, either deep x-ray or radium implantation. Recently increasing favor has accrued to the application of bilateral orchiectomy and oral administration of diethylstilbestrol. Deep x-ray therapy is still used in a few cases in which pain persists in the metastatic manifestations of the disease. In advanced cases, transurethral resection, orchiectomy, and hormone therapy are followed by lower operative mortality, greater longevity, and more marked relief of symptoms.

This communication consists of a report of 130 patients treated at St. Mary's Hospital and Southern Pacific General Hospital between January, 1940 and January, 1946. Thus, we add our observations to the experiences of others recorded in the excellent articles already published on this subject.

INCIDENCE

It has been repeatedly stated that approximately 20 per cent of the pathological specimens removed by prostatectomy reveal the presence of carcinoma. Out of 337 specimens removed by suprapubic or perineal prostatectomy at our two hospitals during the past 5 years, 8.4 per cent showed carcinomatous involvement. In a certain number of these, the presence of malignancy was suspected because of the hard consistency of the gland to rectal palpation; in many, clinical evidence was negative for cancer. According to Kahler, in 51 per cent of autopsied cases in which a clinical or pathological diagnosis of prostatic cancer had been made, metastases were encountered. These may appear in any part or tissue of the body, but have a predilection for the bony pelvis, spine, vertebrae, long bones, and lungs. They may also involve the testes and epididymes by retrograde lymph transport.

The current concept of carcinoma of the prostate is that it may coexist with simple hypertrophy and inflammation, and does not represent carcinomatous degeneration of an adenoma. In this series, malignancy was en-

From the Department of Urology of St. Mary's Hospital and Southern Pacific General Hospital. Read before the Second Mexican Cancer Congress, Guadalajara, Mexico, February 6, 1946.

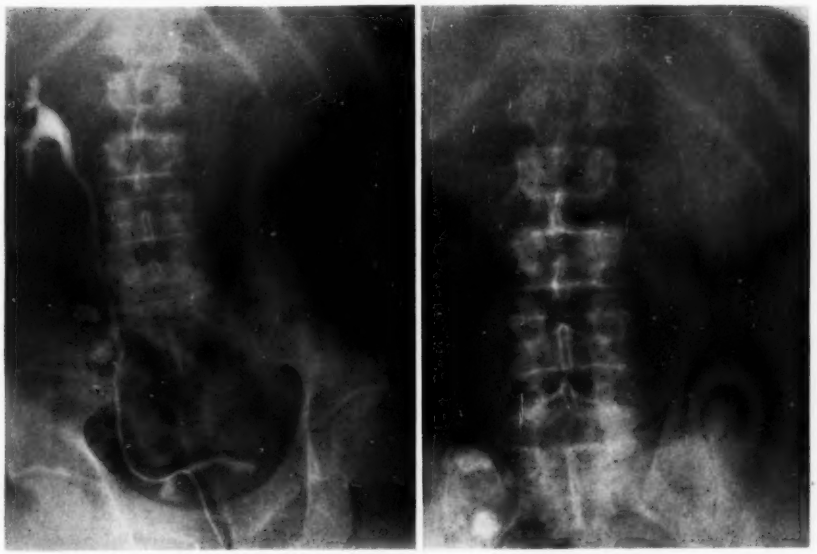

Fig. 1. a, left, Retrograde cystogram showing nodular filling defect in base of bladder due to obstructing prostatic cancer. Note unusual course of catheter in lower right ureter due to pressure of invading prostate. Left ureter could not be catheterized. b, Roentgenogram of lumbar spine demonstrating osteoplastic invasion of fifth lumbar vertebra and sacrum.

countered in 77 of the 533 patients on whom transurethral resection was performed for benign hyperplasia and the smaller bladder neck obstructions. In the great majority of these 77 cases, carcinoma of the prostate was diagnosed prior to operation. A certain number showed the typical clinical picture of carcinoma, as the gland was of stony hard consistency; yet pathological study of the sections removed by transurethral resection failed to demonstrate this lesion. Two such cases are of interest. In the first, castration was not carried out, and resection was repeated because of recurrent obstructive symptoms. At the time of the second intervention, pathological study revealed carcinoma. The second case presented a stony hard area in the region of the apex of the prostate and x-ray evidence of metastasis in the spine. Sections removed were negative for carcinoma. The striking clinical improvement manifested by this patient after resection, orchiectomy, and diethylstilbestrol therapy left little doubt as to the true diagnosis. In all other cases, carcinoma was found in a varying percentage of the sections removed by transurethral resection. Age incidence ranged between 45 and 87 years.

DIAGNOSIS

The onset of carcinoma of the prostate is insidious, and urinary disturbances occur late in the course of the disease. Careful palpation of the gland per rectum is of prime diagnostic importance. The plea for more frequent rectal examination of the prostate in all men over 50 has well been made by the numerous urologists who have written on the subject of prostatic carcinoma. In recent years, an increasing number of internists have referred patients in whom this neoplasm was suspected by reason of the hard consistency of the gland discovered on routine examination by this method. The significance of hard nodules situated in the posterior lobe is accepted by every physician. Unfortunately, similar hard areas located in the lateral and median lobes are inaccessible to digital palpation. Patients who had no reason to consult a urologist presented pain in the back due to bony metastasis in the pelvis and spine. Metastasis from prostatic car-

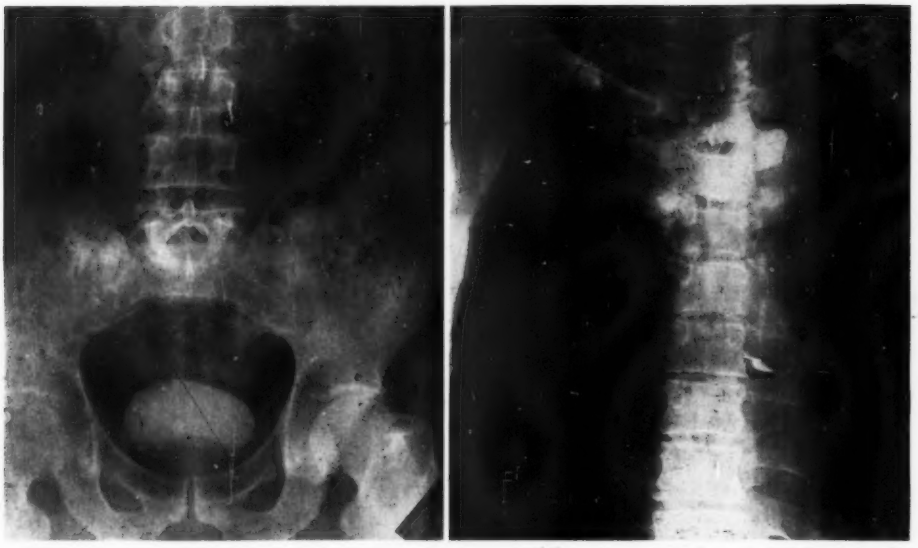

Fig. 2. a, left, Intravenous urogram showing filling defect at base of bladder due to obstructing cancer of prostate b, Roentgenogram of dorsal spine demonstrating osteoplastic and osteolytic involvements of fifth and sixth vertebrae. Patient referred by neurologist because first symptoms appeared in spine.

cinoma was visualized on x-ray examination by the attending orthopedist or neurologist to whom the patient had been referred. In these cases, rectal examination determined the original site of the tumor, and patients were sent to the urologist for treatment. In moderately and fairly well advanced cases, cystoscopy reveals nodular encroachment into the vesical neck and prostatic urethra. The hard consistency of the gland is more noticeable on rectal palpation when cystoscope shaft is in place.

Retrograde or intravenous cystography shows nodular filling defects in the base of the bladder quite different from the picture seen in benign hypertrophy. We routinely carry out intravenous urography, as it affords the opportunity of determining back pressure changes and concomitant lesions in the kidney as well as characteristic filling defects in the base of the bladder. In every instance of suspected carcinoma of the prostate, roentgenograms are made of the long bones, bony pelvis, spine, and lungs in an effort to determine the presence of metastasis. Its appearance is often confused with that of hypertrophic arthritis and other forms of osseous hyperplasia, particularly Paget's disease. I recall a patient treated by a competent internist for hypertrophic arthritis. Complete retention of urine brought this patient to our service, and examination revealed advanced carcinoma of the prostate with metastasis to the spine. The reaction of bone to metastatic carcinomatous invasion is osteoplastic. Normal cancellous structure is replaced by the blurred outlines of new bone formation. Following orchiectomy, the bone usually becomes denser, its outlines smoother and clearer as healing takes place (1).

Determination of the acid and alkaline phosphatase levels, as originally proposed by Scott and Huggins, offered promise in the diagnosis of carcinoma of the prostate with metastasis. However, Huggins' subsequent study of 47 men with advanced prostatic carcinoma showed 50 per cent elevation of phosphatases and 50 per cent normal (4). We have made phosphatase studies in a number of patients presenting this disease, and find it unreliable. In fact, in the majority of cases reported in our series in which blood acid phosphatase tests were carried out, the concentration was found to be within normal limits

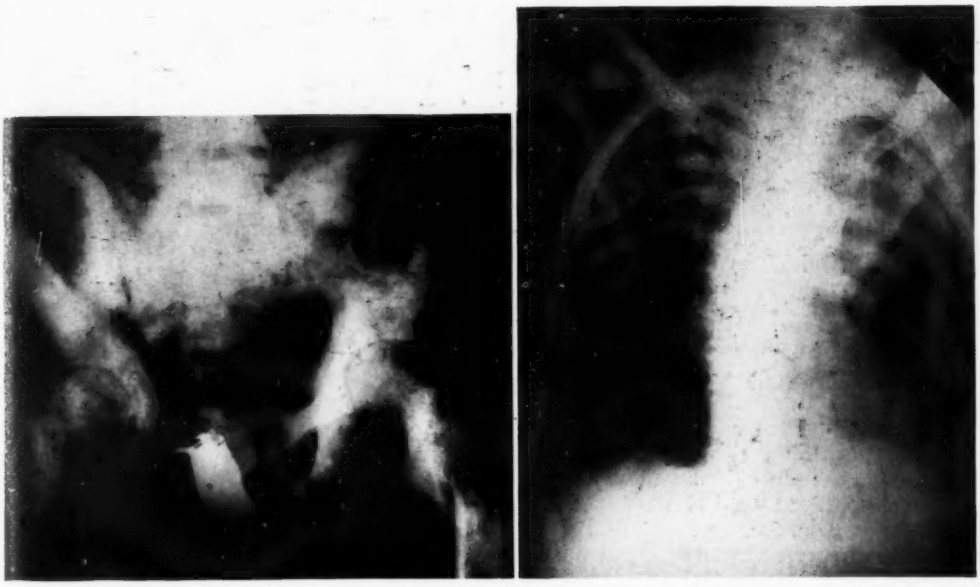

Fig. 3. a, left, Roentgenogram of pelvis showing advanced osteoplastic and osteolytic involvement of bones making up pelvic girdle. Transurethral resection, bilateral orchiectomy and stilbestrol therapy prolonged this patient's life. b, Roentgenogram of chest demonstrating late metastasis in lung and ribs.

When it is elevated, this finding aids in confirming the diagnosis already made by other clinical observations. In addition, it assures the rationale of orchiectomy.

Direct biopsy of prostatic tissue has been used; we do not employ it as a routine, because the piece removed may be free of disease in an otherwise carcinomatous gland; moreover, this intervention may serve to hasten dissemination of cancer cells.

SYMPTOMATOLOGY

Unfortunately, the patient presents no symptoms in the early stages of the disease, at which time carcinoma is usually localized in the posterior lobe. Loss of weight, anemia, cachexia, and pain often precede urinary disturbances. It is at this time that the astute attending physician may detect the elusive disease by carrying out skillful rectal examination. Later, invasion of the vesical neck and posterior urethra takes place, causing frequent, difficult, and painful urination. In cases in which carcinoma occurs concomitantly with benign hypertrophy, the well known obstructive symptoms of prostatism are present. Occasionally, prostatic cancer metastasizes early, and pain resulting from extension to the spine, pelvis, long bones, and lungs are the only manifestations present. Cases have been reported in which the first symptoms were due to metastases occurring in the brain, thyroid, liver, testes, and epididymes. Not infrequently the internist, orthopedist, and neurologist are consulted because pain in the osseous system predominates. These specialists are rapidly becoming familiar with the characteristic roentgen appearance of bony metastasis of cancer of the prostate, and refer more patients to the urologist for present day treatment.

TREATMENT

Radical perineal prostatectomy as proposed by Young and modified by Colston and by Belt is the treatment of choice for eradication of early carcinoma of the prostate. The entire gland including its capsule, the adjacent vesical neck, prostatic urethra, and seminal vesicles are removed *en bloc*. Unfortunately, this operation is of no value in occult carcinoma;

nor does it provide for removal of the regional lymphatics which become involved early (51 per cent according to Kahler). As the disease progresses, encroachment into the prostatic urethra and bladder neck takes place, and the problem becomes primarily and often urgently one of relieving urinary obstruction. At this stage, the disease has advanced to a point far beyond the reach of radical intervention. Until about 1932, removal of obstructing cancerous tissue was accomplished suprapubically or perineally. Since that time, the perfected operation of transurethral resection has proved to be the more benign procedure, even if it must be repeated. By providing an adequate channel for urinary outflow, back pressure on the kidneys is relieved, early death from uremia prevented, and life prolonged. At best, life expectancy in these elderly men is short, surgical risk is poor, and the comfort of the patient is the primary motive. Our good results, added to those reported by many other authors, are a testimonial to the efficacy of this operation. It offers the additional advantage of detecting and relieving concomitant lesions of the bladder, e.g., papillomas and small calculi.

The splendid work of Huggins and his associates on orchiectomy (6) added an effective weapon to combat this incurable disease. Their observations concerning regression of the cancerous process in the gland itself, as well as in its metastatic manifestations in the skeletal system and soft tissues following orchiectomy, were readily accepted and corroborated by numerous surgeons. Some prefer to employ radiation therapy to the testicles rather than orchiectomy; the results of the two procedures are of equal value. Orchiectomy has given us very good results; however, we prefer to relieve urinary obstruction by transurethral resection, as without this auxiliary intervention the patient may succumb from uremia before sufficient regression of the obstructing cancerous gland has taken place. A case in point is that of Dr. H., aged 70 years, who entered the hospital with advanced cancer of the prostate. He presented considerable retention of urine and elevated acid phosphatase. Orchiectomy was performed; transurethral resection was refused, and the patient died from uremia 3 weeks later. One should not depend on orchiectomy and stilbestrol therapy alone. Opinion is divided regarding the best time to perform orchiectomy (8). Some employ it only after metastasis has taken place and is advanced; others contend that it should be carried out as soon as the diagnosis is made. In the presence of metastasis we always advise it, and in active cases associated with pain we recommend its early application.

Further studies of Huggins (5) revealed that in the majority of cases ingestion of stilbestrol caused regression of cancer of the prostate and of its metastatic manifestations throughout the body. This female hormone exerts an antagonistic effect on androgens, which are normal in the prostate and excessive in the presence of cancer of that gland. Hormone therapy (oral diethylstilbestrol) should be instituted as soon as the diagnosis is made. There are certain cases of advanced cancer with extensive metastases in the bony structures and lymph and vascular systems in which pain due to pressure on adjacent nerves is not relieved by orchiectomy or hormone therapy. In these, deep irradiation may be utilized for relief of intractable pain.

ANALYSIS OF CASES

In reviewing our 130 cases on which operation was carried out for carcinoma of the prostate, 12 (10.8 per cent) failed to reveal the presence of cancer in the sections removed by transurethral resection. In many of these, the gland presented stony hard consistency to rectal palpation; there was loss of weight, uremia, cachexia, etc., and x-ray evidence of metastasis in the bony structures and lungs. In some patients, all sections removed demonstrated active carcinoma; in others, it was found in only 1 out of 8 or more sections. When clinical evidence pointed to prostatic cancer, and the pathological specimens were negative for cancer, the acid phosphatase test was of little value to us in clarifying the diagnosis, as has already been pointed out by Huggins and many others. In some cases, a second resection became necessary for relief of recurrent urinary obstruction; later histological examination revealed the elusive carcinoma.

It must be realized that in carrying out transurethral resection one is concerned with

removal of the obstructing tissue alone, and that the cancerous process which was so well detected by rectal palpation may not have involved the intraurethral tissues. Our observations clearly show that in 10 per cent of cases carcinoma of the prostate was absent in tissue removed by resection. Yet in these, the clinical picture was typical of advanced carcinoma. Therefore, in attacking the problem one must be guided by the clinical diagnosis, although one must always strive to secure laboratory substantiation. This was obtained in 90 per cent of our cases; in the 10 per cent in which it was lacking, we felt justified in proceeding with present day methods of relief.

Carcinoma of the prostate was encountered in 28 glands removed by suprapubic enucleation. In the great majority of these, it was not suspected prior to operation. In 8, the gland was fairly hard to rectal palpation, and carcinoma was believed to be present. When early carcinoma of the prostate was suspected, we elected radical perineal prostatectomy in the very early case and transurethral resection in all others. Transurethral resection was carried out in 77 patients. It was necessary to perform secondary resection for recurring obstructive symptoms in 4. Radical perineal prostatectomy was performed in 3 (2.3 per cent). These are living and well 3, 4, and 5 years after operation. Subsequent orchiectomy and stilbestrol therapy was carried out in 2 of these. The fact that so few cases of early carcinoma came to us at a time at which it was possible to carry out radical operation substantiates the opinion of other urologists, that earlier diagnosis should be made by the attending physician. Orchiectomy was carried out in 94 patients. When the favorable results obtained by this beneficent operation were explained to the patient, we had little difficulty in securing his consent. Nine presented no urinary obstructive symptoms, and were treated by orchiectomy alone. We prefer to carry out transurethral resection in cases in which retention is present, and not to rely on orchiectomy to bring about regression of the growth, thereby permitting free urination. It affords the additional advantage of corroborating the diagnosis by histological examination. In certain cases in which we counted on orchiectomy alone, death from uremia ensued. Among those who refused orchiectomy were two physicians.

Thirteen patients were not treated by prostatectomy or transurethral resection. Some of these were in the advanced stages, and died shortly after cystotomy for urinary retention due to impassable obstruction, x-ray therapy for metastasis, and medical care alone. Of the 108 patients on whom operation was carried out, 12 (11 per cent) died within 6 weeks. We wish to comment on the greater mortality following removal of the prostate for cancer (11 per cent) than for benign hypertrophy (3.5 per cent). Two patients succumbed after suprapubic prostatectomy for benign hypertrophy in which carcinoma was encountered, and 10 after transurethral resection for known carcinoma. Causes of death were pulmonary embolism, pneumonia, cardiac collapse, and other complications or intercurrent disease. An important number died of carcinomatosis, and there was no noticeable abatement of the disease process. It is interesting to observe that 7 out of 13 cases in which no operation on the prostate was carried out promptly expired: 5 after medical care alone (45 per cent), 2 after cystotomy for complete retention due to impassable obstruction (100 per cent), and 1 after orchiectomy alone (11 per cent). The mortality following operative intervention for carcinoma of the prostate is high because we are dealing with patients in the advanced stages of cancer, debilitated by toxemia and varying degrees of uremia. Except in the occasional early case, treatment consisting of transurethral resection, orchiectomy and hormone therapy is merely palliative. However, the relief of symptoms and prolongation of life which it offers makes the risk worth while—11 per cent mortality as shown by the review of this series of cases.

Out of 108 cases in which surgical intervention was carried out for carcinoma of the prostate, we were able to follow 50. In these, orchiectomy and stilbestrol therapy supplemented transurethral resection, radical perineal prostatectomy, and suprapubic enucleation. Eighty per cent were definitely improved; 20 per cent showed little if any amelioration and these rapidly succumbed to the disease.

Since 1942, when orchiectomy and stilbestrol therapy were proposed as an additional means of combating this disease, 9 survived three years, 14 two years, 10 one year, and 17 less than one year. Of unusual interest is the case of Mr. A., aged 76 years, who was completely disabled because of difficult urination and intense pain due to metastasis. He had been abandoned to morphine therapy. Transurethral resection, orchiectomy, and stilbestrol therapy were carried out 1 year ago. Relief was so great that he returned as a shipyard worker within 6 weeks and has been active ever since. A number of similar cases in this series bear evidence to the efficacy of this treatment. Of particular interest is the case of Mr. D., colored, aged 65 years. On December 1, 1944, transurethral resection and bilateral orchiectomy were carried out. The removed sections showed active carcinoma. Recheck examination was made on September 21, 1945, at which time digital and cystoscopic investigation revealed clinical absence of carcinoma. A number of patients who refused orchiectomy at the time of transurethral resection accepted it 1 to 2 years later on account of increasing pain due to bony metastasis which persisted in spite of stilbestrol therapy. Of equal interest is the case of Mr. J. K., aged 58 years, on whom suprapubic prostatectomy was carried out in March, 1942. Carcinoma was encountered within the adenoma and bony metastases developed 1 year later. He refused orchiectomy, was placed on diethylstilbestrol therapy, and is still enjoying good health.

SUMMARY

One hundred thirty cases of carcinoma of the prostate treated between 1940 and 1946 are reviewed. Operative intervention was employed in 108: transurethral resection in 77, radical perineal prostatectomy in 3, and suprapubic enucleation in 28. Eleven advanced cases received medical care or x-ray therapy only. In 2, cystotomy for relief of retention due to impassable obstruction, in 9, orchiectomy and stilbestrol therapy alone were carried out.

Twenty-eight of the 337 specimens of prostate removed for benign hypertrophy in which carcinoma was not suspected revealed carcinoma (8.4 per cent).

Mortality for operative interventions for cancer of the prostate is 11 per cent in 108 cases, as compared with 3.5 per cent in 337 prostatectomies for benign adenoma during the past 5 years.

Rectal palpation is still the sole criterion of early diagnosis. Only 3 in our series were detected early enough to justify radical perineal prostatectomy. Cystoscopy, cystography, and x-ray examination of the skeletal system and lungs corroborated the presence of varying stages of cancer with or without metastasis. Elevation of blood acid phosphatase, although of great aid when present, was of no value in elusive disease.

In 11 per cent of our 77 patients treated by transurethral resection which presented positive clinical evidence of carcinoma, histological examination of the pathological specimens failed to reveal the presence of cancer. The favorable subsequent clinical course warrants our contention that one should proceed with transurethral resection, orchiectomy, and stilbestrol therapy in such cases.

Radical perineal prostatectomy is the treatment of choice in early carcinoma. Unfortunately, it is of no value in occult cancer and does not provide for removal of regional lymphatics. Transurethral resection, supplemented by stilbestrol therapy, orchiectomy and deep irradiation for intractable metastatic pain resulted in definite improvement and increased longevity in 80 per cent of our patients.

Although we are dealing with a progressively fatal disease, the present day palliative measures at our command are justified as they relieve urinary obstruction and ameliorate toxic symptoms, thereby prolonging life.

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STUDIES ON ANURIA

Effect of Infusion Fluids and Diuretics on the Anuria Resulting from Severe Burns

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IF an anuria is not relieved by physiological processes or by therapy, death invariably ensues. Many types of diuretic agents and infusion fluids have been employed with varying degrees of success to relieve anuria or oliguria following hemoglobinemia. This study attempts to evaluate the agents and fluids which have been used on human beings. We have found that some agents were far more effective than others and that the accepted therapeutic practice was not always the most effective. Although, the agent found to be most effective in our study has been infrequently employed, it was successful when used in a limited number of human cases. We believe, therefore, that our results can be applied in the treatment of patients with anurias following severe burns, transfusion reactions, crush syndrome, and in toxic hemolytic anurias, and we therefore submit our experiences and our results to the medical profession.

In an earlier study of anuria in experimental shock, we differentiated three distinct types which we designated the "burn," "crush," and "hemorrhage" (reduced blood volume) anurias (17). The "burn" anuria was selected for the more extensive studies because it is acute and develops rapidly, and therefore may be studied more easily in the experimental animal. Severe thermal trauma produces a severe hemoglobinemia; consequently, if the kidney is able to excrete urine, hemoglobinuria follows. In patients burned in the Cocoanut Grove disaster, Shen and co-workers described hemoglobinemia and hemoglobinuria. We believe that a review of the literature (5, 10, 19, 20) together with our data indicates that the damaged renal function produced by burns is similar to that following hemolysis from incompatible blood transfusion (transfusion kidney), blackwater fever, and other hemolytic diseases. Some features are also similar to the renal impairment in the crush syndrome. The common factor in all of these cases is an intravascular hemolysis due to the sudden and rapid destruction of erythrocytes or muscle cells. This destruction liberates large amounts of hemoglobin or myoglobin and fragments of destroyed cells into the systemic circulation. In addition, the factor of damage to renal tubular epithelial cells by anoxia and toxins plays a rôle. Ross states that the mortality rate is high in most diseases associated with hemoglobinuria.

In our studies of anurias which followed experimental procedures leading to shock we felt the need for determining the relative effectiveness of present methods of relieving these anurias. A number of workers in England have observed and treated impairment of renal function due to crush or compression of limbs ("crush kidney syndrome"). Bywaters in 1944 has suggested the following therapy for the crush kidney: administration of fluids and alkali, concentrated serum, mercurial diuretics, and, in established renal failure, decapsulation. Maitland in 1941 (12) recommended the use of isotonic sodium sulfate for the treatment of the crush kidney and later reported good results (13). Shepherd in 1942 used a slow intravenous drip of isotonic sodium sulfate solution and, in view of the tubular renal lesions, was against giving any drastic diuretics such as mercurials. He feels that "blood transfusion is contraindicated, as the inevitable degree of hemolysis will throw additional strain on secretion."

We felt that conclusions as to the most effective treatment are difficult to establish

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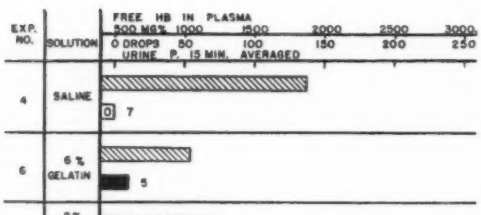

Chart 1. The shaded columns represent the amount of free hemoglobin in the plasma, in milligrams per cent. The black columns represent the average drops of urine per 15 minute intervals, excreted after the last infusion.

from observations on human subjects alone, and Bywaters bears this point out in his article by saying that little is known about the effects of therapy.

Experimental procedure. Large healthy male dogs were used for all experiments. They were kept under deep nembutal anesthesia throughout the experimental period. The abdomen was opened and each ureter was cannulated and connected to a sensitive drop recorder and counter (16), which registered on a kymograph the urine excreted from each kidney. Blood pressure was recorded on the same kymograph so that an immediate correlation between blood pressure and urine excretion was possible and the effects of the burn and of the treatment could be followed closely. Repeated determinations of plasma carbon dioxide, hemoglobin, hematocrit, and free hemoglobin in the plasma were done. In a number of experiments kidney function tests were performed; these were glomerular filtration rate using mannitol clearance, and effective renal plasma flow using para-amino hippuric acid clearance (7). A number of preliminary experiments were required to develop a type of burn with reproducible renal damage. Not every burn will produce the "burn anuria," but only extensive and severe thermal trauma.

The severity of the anuria in most burn experiments could be correlated with the degree of hemoglobinemia. Therefore, the amount of free hemoglobin in the plasma was used as a basis for comparing the therapeutic value of infusion fluids and diuretics. In preliminary experiments isotonic saline solution was used for the control infusions. The procedure used in most experiments was as follows: A control period of 1 to 2 hours; when the kidneys excreted at a constant rate the animals were burned severely. Complete cessation of urine flow occurred within 5 to 10 minutes in all experiments. The onset of this type of anuria is most rapid compared to that of "crush" and "hemorrhage" anuria. Therapy was started an hour after the burn. At that time blood samples were drawn for chemical studies. The first intravenous infusion of 15 cubic centimeters per kilogram was given at the rate of 10 to 15 cubic centimeters per minute. Two additional infusions were given at 30 minute intervals. At the termination of the last infusion additional chemical studies were made.

Results. The total number of experiments performed for this paper is 68. Two control experiments of 18 and 32 hours' duration, and 23 thermal trauma experiments were reported in an earlier paper (17). From this work, we were able to devise an experimental procedure for the 43 studies presented in this paper on the treatment of the burn anuria. Included in this latter group are a few studies on kidney function before and after the use of the most effective therapeutic agent, isotonic sodium sulfate.

Chart 1 compares the effect of infusion fluids on urine excretion with the amount of free hemoglobin in the plasma after the burn. In Experiment 4, after the burn, the amount of plasma hemoglobin was 1,870 milligrams per cent. At this relatively high concentration of hemoglobin no urine was excreted following

the intravenous infusions of saline. In Experiment 2 (not shown on Chart 1) a small amount of urine, 14 drops per 15 minutes, was excreted after the infusion of saline. However, the free hemoglobin was only 580 milligrams per cent. We have found that saline has very little beneficial effect on the anuria when the free hemoglobin in the plasma is above 1200 milligrams per cent. In Experiment 6 (Chart 1) 6 per cent gelatin had a slight diuretic effect when the free hemoglobin was 1100 milligrams per cent. In Experiment 8, 2 per cent urea in 6 per cent gelatin had a slightly better effect than gelatin alone, although the plasma hemoglobin was higher. In Experiment 9, 2 per cent urea in saline had an even more marked diuretic effect when the free hemoglobin was as high as 1850 milligrams per cent. The addition of urea made saline solution an efficient diuretic. This is shown in Experiment 4, in which no urine was excreted, although the levels of free hemoglobin were similar in Experiments 4 and 9. In Experiment 10, we found that Ringer's lactate solution was superior to saline or gelatin. It had some beneficial effect on urinary flow, even though the plasma hemoglobin was as high as 1540 milligrams per cent. The therapeutic value of saline was improved by addition of caffeine. In Experiment 12, a distinct diuretic action was shown by this combination, when the free hemoglobin in the plasma was 1710 milligrams per cent. A combination of 2 per cent urea, 5 per cent dextrose, and caffeine in 1/12 molar lactate solution was somewhat toxic, and we discontinued further attempts with this "shot gun" type of therapy. In Experiment 15 we found that 2 per cent urea in 1/6 molar sodium lactate solution had no effect on the anuria produced when the animal was severely damaged (free Hb was 2700 mgm. %).

At this stage of our study, we concluded that certain infusion fluids were more effective than others in overcoming the anuria of burns, but that a limit could be reached in effectiveness when such severe burns were produced that the plasma hemoglobin was extremely high. In Experiment 19 on Chart 2, heparinized plasma produced a distinct excretion of urine when the free hemoglobin in the plasma was only 1195 milligrams per cent. But when the

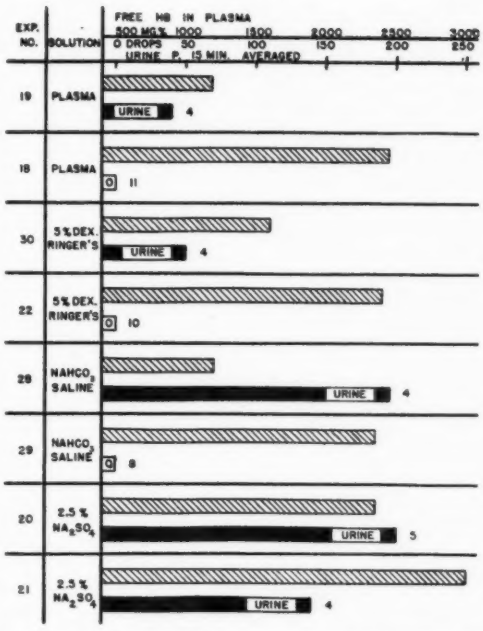
EXP. NO.
SOLUTION
FREE HB IN PLASMA
300 MG.% 1000 1300 2000 2300 3000
0 DROPS 50 100 150 200 250
URINE P. 15 MIN. AVERAGED
19 PLASMA URINE 4
18 PLASMA 0 11
30 5% DEX. RINGER'S URINE 4
22 5% DEX. RINGER'S 0 10
28 NAHCO3 SALINE URINE 4
29 NAHCO3 SALINE 0 8
20 2.5% NA2SO4 URINE 5
21 2.5% NA2SO4 URINE 4

Chart 2. The shaded columns represent the amount of free hemoglobin in the plasma, in milligrams per cent. The black columns represent the average drops of urine per 15 minute intervals, excreted after the last infusion.

kidneys were more severely damaged as in Experiment 18, in which the free hemoglobin was 2450 milligrams per cent, no urine was excreted after three infusions of plasma. Five per cent dextrose in Ringer's solution was more effective in Experiment 30 than saline alone in Experiment 4, but when the animal was more severely damaged, as in Experiment 22, dextrose Ringer's had no effect. The next type of fluid tried was a combination of 0.87 per cent sodium bicarbonate in saline. When free hemoglobin was low following the burn, this mixture had a marked diuretic action as shown in Experiment 28 (plasma hemoglobin was 1170 milligrams per cent, and urine flow 195 drops per 15 minutes). However, when the free hemoglobin was 2300 milligrams per cent as in Experiment 29, bicarbonate and saline had no effect on the burn anuria. We finally tried isotonic sodium sulfate solution, as suggested by Maitland for the treatment of the crush kidney syndrome (12). Experiment

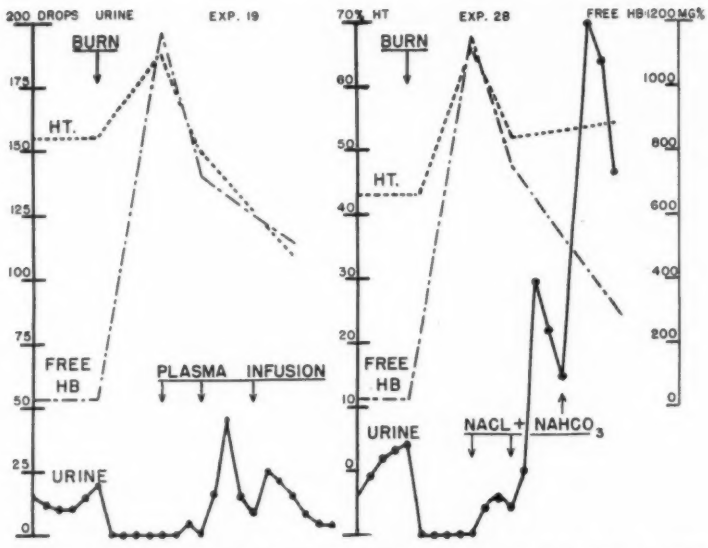

Chart 3. Urine from both kidneys is recorded as the average number of drops per 15 minutes. Plasma hemoglobin (free Hb), is recorded in milligrams per cent, and the hematocrit (Ht) as per cent.

32 showed that this fluid could produce a marked diuresis, even when the amount of free hemoglobin was as high as 2250 milligrams per cent. In Experiment 20, isotonic sodium sulfate solution was used; free hemoglobin was 2350 milligrams per cent, and urine was excreted at the rate of 200 drops per 15 minutes. In Experiment 21, free hemoglobin was 2980 milligrams per cent, yet the kidneys excreted 140 drops per 15 minutes after three infusions of sodium sulfate. To date, this fluid has been the only agent that will, in all cases, stimulate the kidneys to excrete after a severe burn. It is the only fluid that has been found to have a marked beneficial effect on the burn anuria when the free hemoglobin in the plasma is above 2000 milligrams per cent, and no failure of response to sodium sulfate infusion was encountered in any of our experiments.

A closer comparison of certain experiments is enlightening when they are selected on the basis of similar concentrations of plasma hemoglobin after the burn. Chart 3 illustrates the effect on the burn anuria of plasma in Experiment 19, and the effect of saline plus an alkali ($Na\ HCO_3$) in Experiment 28.

The control values in Experiment 19 (left) are as follows: urine, 14 drops per 15 minutes, hematocrit, 52 per cent, free hemoglobin, 10 to 20 milligrams per cent. One hour after the burn the hematocrit had risen to 65 per cent, free hemoglobin was 1175 milligrams per cent and urine excretion stopped. The first plasma infusion caused only a slight excretion of urine, less than 1 cubic centimeter; the second infusion was followed by an average of 19 drops per 15 minutes, but after the third infusion urine secretion fell to 12 drops per 15 minutes. The total urine excreted after a total plasma infusion of 750 cubic centimeters was only 19 cubic centimeters over a period of 3½ hours. There was, however, a marked decrease in both plasma hemoglobin and hematocrit. This was probably due to the diluting effect of the plasma only. The control values in Experiment 28 were: urine, 20 drops per 15 minutes, hematocrit, 43.5 per cent, free hemoglobin, 15 to 20 milligrams per cent. One hour after the burn the hematocrit had risen to 66 per cent, the free hemoglobin to 1170 milligrams per cent (similar to the concentrations in the plasma experiment), and urine excre-

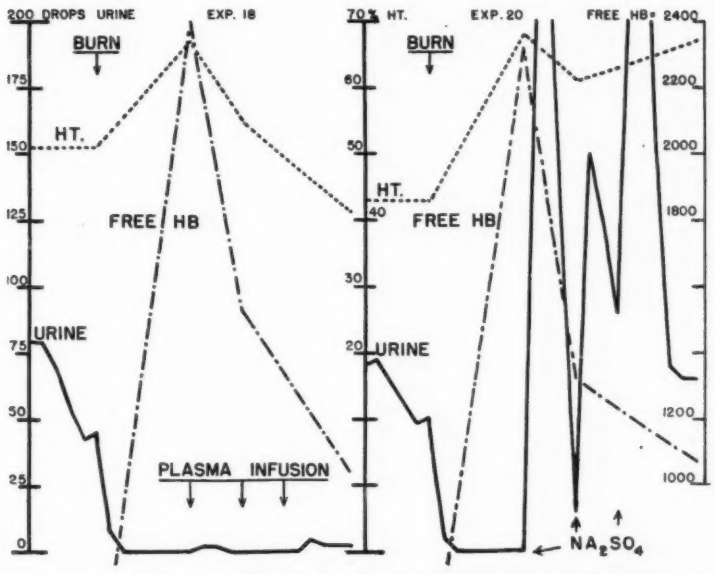

Chart 4. Urine from both kidneys is recorded as the average number of drops per 15 minutes. Plasma hemoglobin (Free Hb) is recorded in milligrams per cent, and the hematocrit (Ht) as per cent.

tion had dropped to zero. The first infusion of the sodium bicarbonate plus sodium chloride solution produced only a small amount of urine, averaging 13 drops per 15 minutes and a total volume of 6 cubic centimeters. The second infusion produced considerably more urine, 67 drops per 15 minutes and a total volume of 32 cubic centimeters, and the third infusion an average of 195 drops per 15 minutes and a total volume of 92 cubic centimeters of urine. Altogether, 130 cubic centimeters of urine was excreted in response to 708 cubic centimeters of infusion fluid. The drop in free hemoglobin is greater in this experiment than in the previous one in which plasma was used. There was a 75 per cent decrease in the free hemoglobin and a 12.0 per cent decrease in the hematocrit. In Experiment 19, a 60 per cent decrease in free hemoglobin, but a 31 per cent decrease in hematocrit occurred.

Chart 4 compares the results of infusions of plasma and isotonic sodium sulfate (Experiments 18 and 20). Both animals were given more severe burns than those in Chart 3. The values for free hemoglobin after the burn were 2450 and 2350 milligrams per cent, respectively. The three plasma infusions in Experiment 18, totaling 795 cubic centimeters, produced less than 1 cubic centimeter of urine. The three sodium sulfate infusions in Experiment 20, totaling 570 cubic centimeters, produced 266 cubic centimeters of urine, and an immediate diuretic effect was obtained with the first infusion. In the experiment in which plasma was used, the decrease of the hematocrit was 25 per cent, and the decrease in plasma hemoglobin was 59 per cent. On the other hand when sodium sulfate was used the decrease in hematocrit was only 5 per cent although free hemoglobin decreased 49 per cent. This seems to indicate that more free hemoglobin was removed from the blood following sodium sulfate infusion than after plasma infusion, and that the action of the plasma was largely that of a diluent of the blood.

Table I is a summary of all experiments reported in this paper, grouped according to the therapeutic agent employed. The experiments which have been discussed in detail

TABLE I.—SUMMARY OF ALL EXPERIMENTS ON EFFECT OF DIURETICS ON THE BURN ANURIA

Exp. No.	Fluid or substance injected	No. injections	Free Hb in plasma	Per cent increase hematocr.	Drops of urine* p. 15 min
18	Plasma	3	2450	16	5
19	Plasma	3	1175	13	25
22	5% glucose saline	3	2400	14	0
12	Saline	1	1710	13	2
5	Saline	1	1240	10	3
4	Saline	1	1870	14	4
3	Saline	1	550	18	6
2	Saline	1	580	17	30
1	Saline	Const. inj.	3080	10	∞
27	5% hypertonic saline	3	1090	11	32
28	Bicarb. saline	3	1170	22	390
29	Bicarb. saline	3	2325	24	0
16	Sodium lactate	1	1585	13	31
17	Sodium lactate	2	2875	19	3
10	Ringer's lactate	1	1540	15	9
11	Urea, glucose, lactate	1	1350	17	136
13	Caffeine, urea, glucose lactate	1	1725	18	303
14	Vitamins, lactate	1	1140	12.5	62
15	Urea, vitamin, lactate	2	2740	15	0
12	Caffeine-saline	1	1710	13	31
13	Caffeine-lactate	1	1725	18	46
15	Caffeine-lactate	2	2730	15	0
12	Mercupurin-saline	2	1710	13	34
18	Mercupurin-plasma	1	2450	16	2
18	Aminophyllin-plasma	1	2450	16	3
20	Sodium sulfate	3	2350	26	392
21	Sodium sulfate	3	2980	13	281
32	Sodum sulfate	3	2250	10	582
33	Sodium sulfate control	3	0	0	1150
34	Sodium sulfate	2	2175	15	594
35	Sodium sulfate	2	2650	11	485
36	Sodium sulfate	2	1550	17	1712
37	Sodium sulfate	2	3032	14	402
38	Sodium sulfate	2	1950	12	832
39	Sodium sulfate	2	1108	13	780
40	Sodium sulfate	2	1992	11	926
41	Sodium sulfate	2	3032	16	978
42	Sodium sulfate	2	2325	14	473
43	Sodium sulfate	2	4096	11	129
6	Gelatin	1	1042	21	18
7	Urea-gelatin	1	882	23	417
8	Urea-gelatin	1	1265	18	49
9	Urea-saline	1	1850	9	222
13	Urea-lactate	2	2730	15	0
14	Lactate-vitamins C, B_1, B_2, B_6, nicotinic acid	1	1140	12.5	62
15	Lactate, vitamins C, B_2	2	2730	15	0
17	Lactate, vitamins B_1, B_2, nicotinic acid	2	2875	19	0
26	Tyrode	3	907	19	288
30	5% Glucose-Ringer	3	1650	16	144

*Averages.

were selected from this group on the basis that they demonstrated the pertinent findings of our study, while the remaining experiments are confirmatory. Attention should be drawn to the agent employed, to the amount of free hemoglobin in the plasma after the burn, and to the amount of urine excreted. It will be noted that other diuretic agents had little or no effect when the damage to the kidneys was great. These agents were mercupurine, aminophylline, thiamine chloride, ascorbic acid, niacine, and vitamin B_2 and B_6.

Kidney function tests were performed in the sodium sulfate treated animal only, because that diuretic agent was the only one capable of stimulating sufficient urine excretion for these tests, even in the severest type of burn. Table II gives the significant experimental data obtained, when glomerular filtration rate was studied before and after the thermal trauma and subsequent infusion of sodium sulfate. In the control Experiment G F 1 there was a decrease in filtration rate of 12 per cent, although no trauma was inflicted upon the animal, except that of the anesthesia and the operative procedures. In Experiment G F 2 an 82 per cent decrease in rate occurred, but in G F 3 with a slightly higher plasma hemoglobin, the decrease was only 44 per cent. It should be noted that while the decreases quoted above were decreases from the control values, the differ-

TABLE II.—EFFECT OF BURN AND SUBSEQUENT INFUSION OF ISOTONIC SODIUM SULFATE SOLUTION ON GLOMERULAR FILTRATION RATE (G. F.)

Exp't No.	Procedure	Free Hb in plasma	Per cent change of G F	Drops of urine in 15 min. periods averages
G F 1	Control $+Na_2SO_4$	0	−12	1150
G F 2	Burn $+Na_2SO_4$	2175	−82	594
G F 3	Burn $+Na_2SO_4$	2650	−44	862
G F 4	Burn $+Na_2SO_4$ +Plasma	1550	−45	1712
G F 5	Burn $+Na_2SO_4$ +Plasma	3032	−81	402

TABLE III.—EFFECT OF BURN AND SUBSEQUENT INFUSION OF ISOTONIC SODIUM SULFATE SOLUTION ON COMBINED KIDNEY FUNCTION TESTS

Experiment No.	Free Hb in plasma	Control filtration fraction	After burn $+Na_2SO_4$ filtration fraction	Per cent change in filtration fraction	Per cent change in G. F.	Per cent change in PAH
PAH 1	1950	.393	.618	+57	−44	−64
PAH 2	1108	.286	.433	+51	−74	−84
PAH 3	1992	.301	.393	+30	−35	−50
PAH 4	3032	.259	.443	+71	−34	−62
PAH 5	2325	.273	.199	−27	−52	−33

ences from 100 per cent represent absolute increases from the anuria previous to infusion with sodium sulfate. A combination of sodium sulfate and plasma did not improve the filtration rates over those obtained with sodium sulfate alone, as shown in Experiments G F 4 and 5. In all experiments with sodium sulfate the volumes of urine excreted were excellent as compared with the control volumes.

Table III summarizes the data obtained when both glomerular filtration and effective renal plasma flow were studied before and after the burn and subsequent treatment with isotonic sodium sulfate solution. The first four experiments showed similar results, a greater decrease in renal plasma flow than in glomerular filtration rate, while in Experiment PAH 5, the opposite occurred. The greater change in renal plasma flow in Experiments PAH 1 to 4 was demonstrated by a marked increase in filtration fraction, as shown in the table. Two factors which may cause an elevated filtration fraction are, first, a vasoconstriction of the renal arteries and, second, a marked damage to the renal tubules. Both are probably responsible for our results because the renal tubules are damaged and may be blocked in renal insufficiency associated with hemoglobinuria (15), and vasoconstriction occurs after injections of hemoglobin (14).

DISCUSSION

In the present studies, we were able to produce an acute anuria in dogs which was treated effectively in every instance with isotonic sodium sulfate, while alkali solutions were distinctly inferior. This was surprising, because many authorities recommend the use of alkaline solutions, and these are widely used at present in an effort to alkalinize the urine in patients with hemoglobinuria from transfusion reaction (4), blackwater fever (19), and crush syndrome (3). In a relatively recent article, Lund recommends the use of alkalies (sodium bicarbonate or sodium lactate) for the treatment of hemoglobinemia and hemoglobinuria in occasional cases of very extensive deep burns (10). We will not deny that in many cases, alkali treatment is sufficient; our experiments show that alkaline solutions are effective when the free hemoglobin in the plasma is below 1500 milligrams per cent. Above this level, however, isotonic sodium sulfate infusion is necessary to start the excretion of urine.

Recently Maegraith and Havard warned strongly against the use of intensive alkali treatment in black water fever. They claim that the mortality of blackwater fever has not diminished since intensive alkali treatment was introduced. They also state: "The persistence of the high mortality in blackwater fever shows that any benefit that intensive alkali treatment may have for individual patients is counterbalanced by the deleterious, in fact, fatal, effects it has on others." The danger lies in the production of an alkalosis and this condition may be sufficient to kill the patient.

A careful review of the literature as to the dangers of alkalosis to kidney function reveals

that many observers were cognizant of this fact. Kirsner and Palmer described a number of patients with peptic ulcer who had normal renal function before treatment with calcium carbonate, developing markedly depressed renal function during alkalosis. The Army Malaria Research Unit at Oxford (1) recently described the effects of large doses of alkali in normal men and found that all subjects had disturbances of renal functions. Their conclusion was that large doses of alkali should not be administered in a condition in which renal failure may supervene.

Considerable disagreement is present as to the mechanism of impaired renal function in the presence of hemoglobinemia and hemoglobinuria (19). The most persistent theory, first introduced by Baker and Dodds (2), is that acidosis occurs in many cases of hemoglobinemia and that the hemoglobin damages the kidney only if the urine is acid, due to the precipitation of acid hematin in the renal tubules with subsequent mechanical blockage of urine flow. This is the basis of the alkali therapy. Wakeman and co-workers in 1932 were first to question this theory in conjunction with blackwater fever. They state, "No support has been found for the theory that acidosis occurs in blackwater fever to offer an indication for alkaline therapy. The administration of bicarbonate in the cases described led to the development of alkalosis." Another very important piece of work frequently overlooked is that of Foy and Kondi who described cases of anuria frequently developing in patients who had slight hemolysis and passed alkaline urines, and other patients who failed to develop anuria, although they had marked hemolysis with acid urine (6). In 1943 these men carefully examined the alkalization hypothesis and concluded that there was insufficient evidence to warrant any statement as to the efficiency of alkali solutions in either preventing or relieving the oliguria and anuria in blackwater fever, incompatible transfusions and crush injuries (5).

What are the dangers of the use of isotonic sodium sulfate? This solution has consistently been nontoxic in all of our experiments. Peters states in a recent review: "Because of the efficiency with which sulfate is excreted and its comparative physiological inactivity, its salts have a strong diuretic effect." The sulfate ions, when being excreted, preserve the chloride ion, while many other diuretics cause a depletion of chloride ion. Therefore, in cases where there is a possible diminution of chloride concentration as in burns (8), sodium sulfate is the diuretic agent of choice, due to its mechanism of conserving chloride ion.

Relatively large amounts of isotonic sodium sulfate have been effective in preventing the anuria in the crush syndrome. Maitland originally suggested the use of sodium sulfate up to a maximum of 3 liters per day in man with crush injuries, given by constant drip intravenously (12). In several cases a total amount of 8 liters was given during the first 11 days, with complete recovery (13). We believe that it might be possible to give an initial injection of sodium sulfate to start the urine flow and then follow this by other diuretic agents. In Experiment 43 we obtained the highest level of plasma hemoglobin, 4096, milligrams per cent. The first injection of sodium sulfate caused a slight excretion of urine. The plasma hemoglobin was lowered to 3,300 milligrams per cent, ½ hour after the injection. After this, an injection of 8 per cent gelatin solution was able to stimulate some urine formation. This agent was one of the poorer types of diuretics, yet it was able to cause urine excretion when the plasma hemoglobin was above 3000 milligrams per cent, because of the priming effect of the sodium sulfate.

Ross concludes his excellent review with several important statements which we feel should be stressed: "Hemoglobin must remain in its normal intra-erythrocytic position if health and normal body function are to be maintained. Although capable of transporting oxygen and of sustaining life when in solution in the plasma, the escape of large quantities of hemoglobin from erythrocytes into the plasma is almost invariably followed by adverse symptoms and frequently by death. Red or black urine, the danger signal indicating extensive intravascular hemolysis, must always be taken seriously, its cause determined and appropriate therapeutic measures imme-

diately instituted." Our study indicates that isotonic sodium sulfate is a very valuable therapeutic agent in anurias resulting from the hemoglobinemia of severe burns.

SUMMARY AND CONCLUSIONS

1. With the type of burn employed an acute anuria was produced in which the extent of renal dysfunction could be correlated with the amount of free hemoglobin in the plasma.

2. Plasma and saline were the least effective infusion fluids for combating the anuria. The following solutions, in increasing order of effectiveness, were superior: sodium lactate, 5 per cent dextrose in Ringer's solution, 2 per cent urea in saline, and 0.9 per cent saline with 0.87 per cent sodium bicarbonate. They were effective in instances in which kidney damage was not great.

3. Isotonic sodium sulfate was the most effective agent in combating the burn anuria. It has overcome anuria in all cases in which it was tried. The most severe anuria was one in which the free plasma hemoglobin was over 4000 milligrams per cent.

4. The concentration of free hemoglobin in the plasma was most effectively decreased by the use of sodium sulfate. Infusions of plasma gave an apparent reduction of plasma hemoglobin, but this was demonstrated to be associated with the more prolonged diluting effect of the plasma.

5. The following substances had very little diuretic effect when kidney impairment was great: mercupurine, aminophylline, thiamine chloride, ascorbic acid, nicotinic acid, vitamin B_2 and vitamin B_6.

6. In complete anurias, glomerular filtration rate and effective renal plasma flow were partially restored following the infusion of sodium sulfate. The greatest improvement occurred in the filtration rates.

7. The use of isotonic solutions of sodium sulfate is recommended in the treatment of the anuria of burns and of related anurias.

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DIVERTICULA OF THE STOMACH AND DUODENUM

Treatment by Invagination and Suture

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ALTHOUGH improved roentgenographic technique and an impressive accumulation of medical literature have established the clinical significance of diverticula of the gastrointestinal tract, those of the stomach and duodenum remain relatively rare surgical entities. However, in a period of 1½ years in a Naval Hospital, 5 such cases have been encountered, 2 in the cardiac portion of the stomach and 3 in the third portion of the duodenum. All were diagnosed preoperatively, and all patients have been treated surgically. It is our purpose in presenting these cases to summarize briefly the literature, to state our opinion that the symptoms of diverticula can be entirely relieved by the operation of inversion of the sac without excision, a procedure which has proved successful in our hands and which appeals to us as the safest of all surgical methods, and to consider in some detail several technical features which we have found helpful in its employment.

INCIDENCE

The incidence of diverticula of the alimentary tract cannot be determined, for most of them remain asymptomatic throughout life (15). However, Babcock states that duodenal diverticula are found in 2 per cent of bodies, while Finney gives the frequency as between 1 and 1½ per cent of adults. Lockwood found them in 1.7 per cent of routine gastrointestinal roentgenologic examinations. An incidence of 2.2 per cent was disclosed by Nagel in over 900 autopsies. Warren and Emery report an incidence of 2.3 per cent of patients showing roentgen evidence of gastrointestinal disease. That these figures may be too conservative is suggested by the work of Ackerman who, by packing the duodena of cadavers with plaster of paris, demonstrated diverticula in 11 of 50 subjects. However, Edwards (11) emphasizes that experiments on the dead intestine are entirely without value, pointing out that the strength of the bowel depends upon the strength of its muscular coat and that the strength of muscle lies in its power to contract.

The stomach is infrequently the site of diverticula. Bockus states that over 150 cases have been reported, although in some of these the diagnosis was not established beyond question. Four gastric diverticula were encountered in 3,662 routine autopsies, as reported by Rivers, Stevens, and Kirklin. Shiflett stated they were observed in 0.65 per cent of 786 routine roentgenologic examinations of the stomach. Ten diverticula were removed in 11,234 exploratory operations on the stomach at the Mayo Clinic, according to Schmidt and Walters. Cunha encountered 15 cases of diverticula in the upper end of the stomach in 2 years, a fact indicating that their occurrence may not be too rare.

AGE AND SEX

Most patients having known diverticula are between 50 and 70 years of age. The youngest of Finney's patients was 47, the oldest 78; the average for the group was 63.7 years. Edwards (11) gives 51.9 years as the average age of 25 patients studied by him. In Warren and Emery's series of 103 patients the average age was 58 years, ranging from 30 to 84 years. The literature indicates a slight predilection for the male sex.

ETIOLOGY

Attempts to classify gastrointestinal diverticula have led to the designations true and false, congenital and acquired, primary and secondary, and pulsion and traction. True diverticula are composed of all mural elements, while one or more layers are absent in

the false variety. Congenital types result, by definition, from anomalies of development; they are illustrated in Meckel's diverticulum and, according to Keith, in many diverticula of the stomach The age at which most diverticula become manifest favors their classification as acquired, although it cannot be denied that an inherent weakness may be the underlying factor in such cases. Edwards (8) has identified this inherent weakness with the amuscular intervals in the bowel wall, through which blood vessels pass. Intraluminal tension (pulsion) is of undoubted importance in the development of acquired diverticula, and chronic cough, constipation, vomiting and labor are said to be factors in the genesis of lesions of this type. The so-called traction diverticulum results from adhesions secondary to ulcers and other inflammatory reactions, of which the commoner examples are found in the stomach, i.e., between stomach and gall bladder or stomach and pancreas, and in the colon.

ANATOMY

The frequency of occurrence of diverticula throughout the alimentary tract is said by Van Noort to be in the following order: (1) colon, (2) Meckel's, (3) duodenum (4) pharynx and esophagus, (5) stomach, (6) jejunum, and (7) ileum. Of those arising in the duodenum, three-fourths are found in the second portion (12). In 85 duodenal diverticula recorded by Edwards (9), none originated in the first portion, 65 were in the second portion and 20 sprang from the third portion. Fletcher and Castleden stated that diverticula never occur in the first portion of the duodenum, although Weintraub and Tuggle found them there in 1.7 per cent of their cases, and Lust described 3 in that location in 1 patient. Warren and Emery's 103 duodenal diverticula were located as follows: in the first portion, 8.7 per cent; second portion, 65 per cent; third portion, 15.5 per cent; multiple, 6.8 per cent.

Although Rankin and Martin claimed that in their experience intestinal diverticula are found most frequently opposite the border of the mesentery or in the lateral wall, most authors are in agreement that they occur most commonly in, or close to, the mesenteric border. Edwards (8, 9) on the basis of studies on specimens removed at autopsies and operations, emphasized the constancy with which diverticula are associated with blood vessels. According to him, the mesenteric arterioles bifurcate as they approach the bowel, the branches piercing both muscular coats a short distance from the mesenteric line. The amuscular interval through which the vessels pass has been designated by Edwards as a *locus minoris resistentiae*. These areas of lesser resistance form the anatomical basis for outpouching or herniation of the mucosa. The precise rôle of intraluminal tension in the genesis of diverticula remains speculative.

Three duodenal diverticula operated on by us originated in the posterior wall, a position corresponding to the mesenteric line. The 2 diverticula of the stomach were found on the posterior wall of the cardia near the lesser curvature. The sacs in each case were retroperitoneal and were devoid of muscular fibers, the mucosa forming a delicate translucent wall. The diameter of the smallest was 18 millimeters, while the largest measured 45 millimeters. Definite muscular rings were identified in the necks in all cases. In each instance, a single prominent blood vessel was found crossing over the pouch. However, exploration of this vessel disclosed the constant finding that, as the neck of the diverticulum was approached, it diverged from the sac wall. The small interval thus formed between the blood vessel and the neck proper contained areolar tissue. We believe this anatomical feature to be an important consideration in the surgical management of diverticulum and reference to it will be made under "Treatment."

SYMPTOMS

It is probable that most diverticula remain symptomless, an opinion supported by the frequency with which they are found incidentally at autopsy. Of 57 cases of duodenal diverticula studied by Whipple, not more than half gave symptoms. It is widely held that symptoms due to diverticula are vague and inconstant, and that they do not present a syndrome clear enough to be of aid in diagnosis (10, 12, 14, 18, 23, 28). Lahey cited accu-

mulation of food within the sac and ulceration as the factors determining the symptoms of duodenal diverticulum.

Of the cases treated by us, 3 described their distress as sensations of pressure, tension or fullness. Another complained of moderately sharp pain. The site of distress or pain bore no specific relation to the site of the lesion. Thus, discomfort in the 3 duodenal cases was in the left epigastrium, the midepigastrium and the right umbilical region. One patient with diverticulum of the stomach complained of pain in the midepigastric area. In 2, discomfort usually followed ingestion of a large meal, while 1 denied any relation between food and distress. One patient (Case 3) was able to obtain relief by eating or by taking baking soda. The only feature common to all of our patients was the intermittent character of their discomfort. It appears that the symptoms caused by diverticula of the proximal gastrointestinal tract are not specific, that they share features of other and more frequent pathologic states and that they are of value only insofar as they call for further diagnostic efforts.

DIAGNOSIS

The only reliable method of establishing the presence of a diverticulum of the gastrointestinal tract lies in x-ray examination. Photofluoroscopic and roentgenographic demonstration of a paraluminal sacculus following the administration of barium affords the diagnosis. Pendergrass advised taking a plain film of the abdomen prior to the ingestion of barium in order to differentiate fecaliths and calcified nodes. The diagnostic observations of Costello with reference to lesions of the duodenum include (1) roundness and smoothness in outline of the diverticulum, (2) a connection between diverticulum and lumen demonstrated by emptying the sac by manipulation (palpation), and (3) retention of barium in the sac for periods up to several days. Barium-filled pockets in relation to the duodenum, which *per se* show peristalsis, which empty with the duodenum and which are shallow and wide-mouthed, are apt to be secondary to primary ulcer, the so-called ulcer diverticulum (11). Examination should be made with the patient in the upright, prone, lateral, and oblique positions. Efforts to fill sacs in which drainage is dependent may call for the Trendelenburg position or modification thereof. Guthrie and Brown suggested distending the duodenum with barium by blocking the duodenojejunal juncture with pressure by one hand, while the other hand manipulates the barium through the pylorus. The use of a duodenal tube for injecting barium, as recommended by Buckstein, does not appear to be general.

TREATMENT

While there is some disagreement as to the management of gastric and duodenal diverticula, the weight of opinion favors surgical treatment when symptoms persist or when the sac is large (3, 6, 10, 14, 19). Rankin and Martin prefer medical treatment, but state that surgical intervention seems warranted occasionally. Finney considered that duodenal diverticula should not alter life expectancy and concluded, therefore, that very few of them were of surgical significance.

When abdominal symptoms are present in a patient with a demonstrable diverticulum and when no evidence of other disease of the digestive system can be found, it is our practice to assume the existence of a relationship between symptoms and diverticulum and to advise operation. This is especially true if the sac is large and barium retention is noted by x-ray examination. Several procedures are available for the obliteration of diverticular sacs; invagination (inversion) of the pouch and simple closure of the mural muscular ring have the advantage of simplicity. Resection of the sac and neck or resection of the sac with inversion of the neck is frequently employed. In the face of contraindications to manipulation of the sac itself, gastroenterostomy has occasionally been employed for relief of duodenal diverticulitis and segmental resection for lesions distal to the duodenum. Multiple diverticula may also demand bowel resection.

We prefer to rely on simple inversion of the sac for diverticula of the stomach and duodenum. This procedure is simple, a fact of first importance in attacking lesions of limited accessibility. The advantage of its asepticity is obvious. The hazard of obstruction following

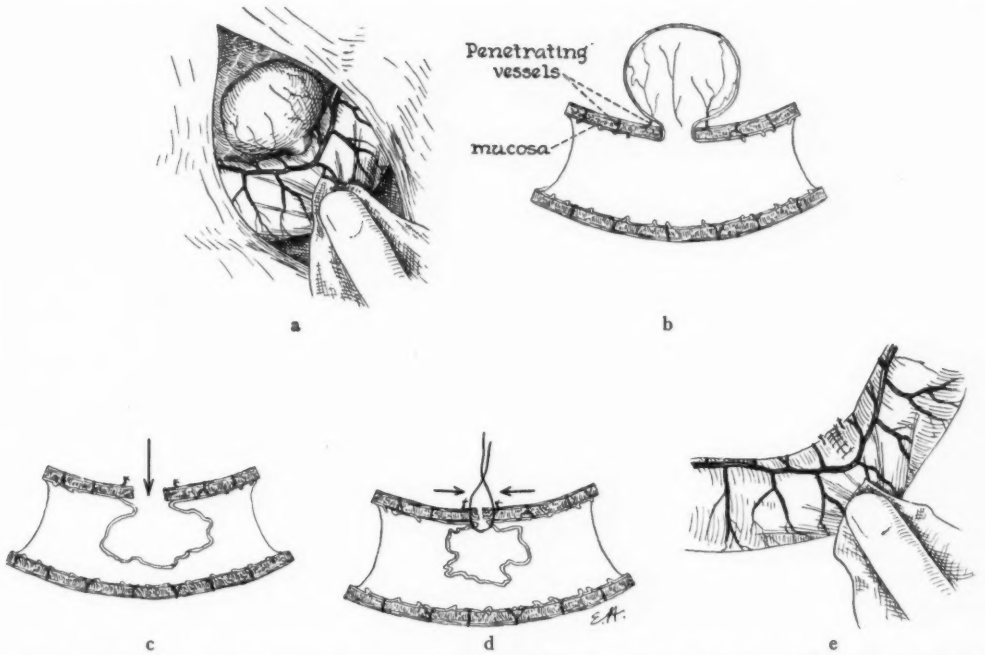


Fig. 1. Diagrammatic view of operation for treatment of diverticulum by invagination. a, Exposure of the diverticulum on the upper surface of the third portion of the duodenum; b, diagrammatic cross section showing the penetrating vessels as they appear on the diverticulum; c, view of the diverticulum after ligation of the penetrating vessels; d, closure of the muscular ring; e, view showing complete suture.

invagination, especially of the larger sacs, is regarded as more academic than practical, an opinion supported by our experience.

OPERATIVE TECHNIQUE

On the evening before operation or early in the morning of operation, a glass of bismuth mixture is given by mouth. This gives the diverticulum a white lining and aids materially in its identification at operation.

The incision for both gastric and duodenal diverticula is made in the midline, and the peritoneum is divided at the site indicated by the roentgen plate. Thus the retroperitoneal space is entered where the white wall of the diverticulum can be identified by pushing aside the loose fatty tissue. Most diverticula which show retention will be found to protrude through a small muscular ring which may be clearly identified by gentle dissection. Usually, one or two small vessels are found to pass from the outside of the muscle layer to the rising surface of the diverticulum. After they have been divided between fine silk ligatures, the sac can be completely inverted within the lumen of the gut and the muscular ring closed with fine silk sutures. The operation is completed by approximating the divided peritoneal layer (Fig. 1).

In the postoperative care, food and fluids by mouth are withheld for 3 to 4 days to permit the effects of the operative trauma to subside.

CASE 1. F. B. M., a 43 year old boatswain in the United States Navy, was admitted to the hospital on April 4, 1944, complaining of intermittent abdominal pain. Upper abdominal distress, described as a feeling of tension, often amounting to pain, had begun in 1934. The symptoms were referred to a point just to the right of the umbilicus; they developed shortly after meals, particularly those consisting of fried or highly seasoned foods and fats. Vomiting was infrequent. The bowels had always been normal. A diagnosis of chronic cholecystitis had been made originally and gall bladder drainage had

been employed many times. Later, the patient was told that he had an ulcer. Recently, when duty in Africa had made it impossible for him to adhere to his restricted diet, the abdominal symptoms had become aggravated. X-ray studies of the gastrointestinal tract were said to have shown an intestinal diverticulum. The past history was not noteworthy. The patient's father had died of cancer. Physical examination showed the patient to be a robust looking, white male in early middle life. Findings at general examination were not remarkable except in the abdomen. There was no distension or free fluid. The liver and spleen were not felt. There was no palpable mass. A circumscribed area of moderate tenderness to deep pressure was present, centering at a point 3 centimeters to the right of the umbilicus. Rebound tenderness was not present nor was the right hypochondrium tender. Laboratory findings were normal. Repeated examinations of the stools for occult blood and bile were negative. A gastrointestinal x-ray series disclosed no abnormality in the esophagus, stomach, or duodenal cap. However, a large diverticulum was present, arising from the duodenum near the duodenojejunal juncture (Fig. 2). Films made 2 and 4 hours after the ingestion of barium showed considerable retention of the medium in the diverticulum. The 24 hour film showed none. On May 2, 1944, laparotomy was performed through an upper abdominal midline incision under continuous spinal metycaine anesthesia. Omental adhesions to the anterior parietal peritoneum were separated. The ligament of Treitz was divided, and the incision was carried somewhat to the right, opening thereby the posterior parietal peritoneum and exposing the terminal duodenum. The diverticulum, measuring 3.5 by 3 by 1.5 centimeters was found arising from the upper, mesial, and posterior surface of the duodenum, 4 centimeters proximal to the duodenomesocolic fold. The neck was small and communicated with the lumen of the gut through a muscular ring 12 millimeters in diameter. It was inverted into the duodenum, and the hiatus in the muscularis was closed over it with interrupted sutures of chromic catgut No. 0. The posterior peritoneum was sutured over the duodenum, and Treitz' ligament was reconstructed. The wound was closed in layers, following the instillation of 25 cubic centimeters of a 20 per cent suspension of microcrystalline sulfathiazole into the retroperitoneal pocket. Healing was complicated by the formation of a subcutaneous hematoma, evacuated on the seventh postoperative day and by a small disruption of the wound on the tenth day, permitting eventration of a walnut-sized mass of omentum. This was repaired at once. The serum protein on this day was 6.8 milligrams per cent. Infection of the abdominal wound (Bacillus coli) developed 12 days following the secondary closure and was quickly controlled by 460,000 units of penicillin. This series of complications forced the intermittent use of gastric (Wangensteen) suction and parenteral fluids until the 22nd postoperative day when the tube was removed and soft diet permitted. Full diet was given after the 27th day. Gastrointestinal x-ray series on June 11, 1944, disclosed no abnormality in the duodenum (Fig. 2). The patient remained free from gastrointestinal symptoms following the operation. He was discharged from the hospital on July 6, 1944.

CASE 2. J. A. C., a 43 year old specialist, first class, in the United States Naval Reserve, was admitted to the hospital May 29, 1944. His complaint of pain in the left upper abdomen was of 2 weeks' duration. The pain was intermittent, being more troublesome after heavy meals, and was described as feeling as though "a pocket of gas was pressing on the heart." It had never been severe, was well localized in the left epigastrium, and had no relationship to the type of food eaten. The sensation of pressure was accompanied by mild shortness of breath. There had been no nausea or vomiting. One year previously, the patient had had a similar single attack, lasting a few days and abating without treatment. His appetite had continued good and he had not lost weight. The bowels were somewhat "irregular." Appendectomy had been performed in 1932. The family history was not relevant. Physical examination showed no abnormal findings, except in the abdomen. An oblique, healed scar was present in the right lower quadrant. No distension or fluid was noted. Deep palpation elicited mild tenderness centering at a point 3 centimeters below the costal border on the left parasternal line. Rebound tenderness was not present. Laboratory findings were normal. Examination of the stools disclosed no ova, parasites, or occult blood. Gastrointestinal x-ray series revealed a large diverticulum arising from the upper surface of the transverse duodenum in its distal third (Fig. 3). The diverticulum remained filled with barium at the end of 4 hours, but there was, otherwise, normal progression of the motor meal. Barium enema disclosed several bud-like diverticula in the transverse, descending, and sigmoid colon. Laparotomy, under continuous spinal metycaine anesthesia, was performed on June 22, 1944. The abdomen was opened through an upper midline incision. A diverticulum 5 centimeters in diameter was found springing from the duodenum at the ligament of Treitz. The pouch was isolated and invaginated through a narrow hiatus in the duodenal muscularis. The muscle opening was closed with a continuous seromuscular suture of chromic catgut No. 0, reinforced with nylon. Five grams of microcrystalline sulfathiazole suspension were placed in the peritoneal cavity. The abdomen was closed in layers with steel alloy wire. Continuous Wangensteen drainage was employed for 48 hours postoperatively, during which time the patient was supported with parenteral fluids. On the second postoperative day liquids were given by mouth. Soft diet was ordered on the fourth day and a full diet was permitted after the ninth day. There were no complaints referrable to the alimentary tract following the operation. Healing was normal. The patient was allowed out of bed on the sixth postoperative day, and was discharged to duty 1 month after operation. Gastro-

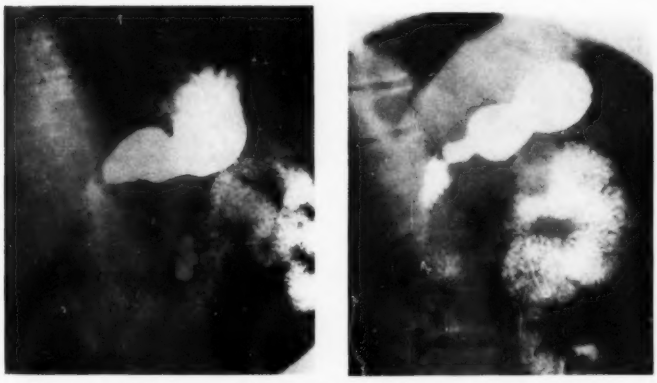


Fig. 2. a, left, Preoperative x-ray film of Case 1; b, postoperative x-ray film 6 weeks after invagination of the diverticulum (official U. S. Naval photograph).

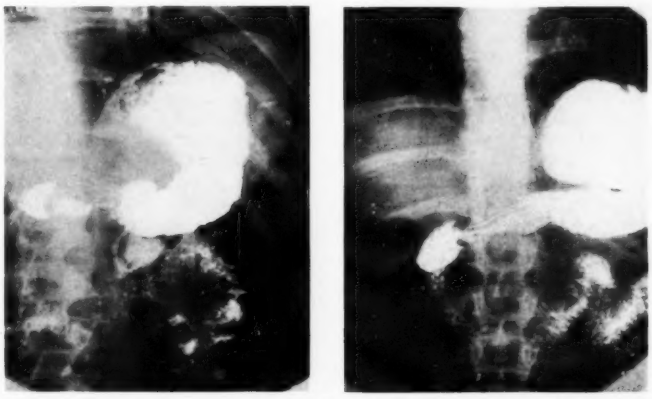


Fig. 3. a, left, Preoperative x-ray film showing diverticulum of the third portion of the duodenum; b, postoperative x-ray film about 15 days following invagination of the diverticulum (official U. S. Naval photograph).

intestinal x-ray examination on July 6, 1944, showed no evidence of diverticulum in the duodenum (Fig. 3). The progression time of the barium was found to be normal.

CASE 3. W. A. S., aged 38 years, a seaman, first class, in the United States Naval Reserve, was admitted to the hospital on April 18, 1945, with the complaint of upper abdominal pain of 1 year's duration. For 6 or 7 years the patient had had frequent attacks of indigestion, the features of which were a feeling of fullness in the stomach, heartburn, and belching. One year previously an especially severe attack had been experienced, during which the patient suffered pain in the upper abdomen, felt nauseated, and vomited. Similar and even more aggravated episodes had followed at shortening intervals. These were not associated with the ingestion of food; rather, they were somewhat relieved by eating and taking soda. The midepigastrium was indicated as the site of discomfort. The bowels were sluggish, moving every 2 or 3 days. There had been no weight loss. The patient smoked 20 cigarettes per day and drank whiskey moderately. His previous medical history was not significant in any particular. His father had had stomach trouble for years. Physical examination showed a normally developed, middle-aged, white male, who presented no abnormality in any particular, except in the abdomen. Moderate tenderness to deep pressure was present in the epigastrium and was greatest at a point halfway between the umbilicus and the ensiform process. The iliac colon was also slightly tender. No organs or masses were palpable. The laboratory findings were normal. Repeated stool specimens contained no oc-

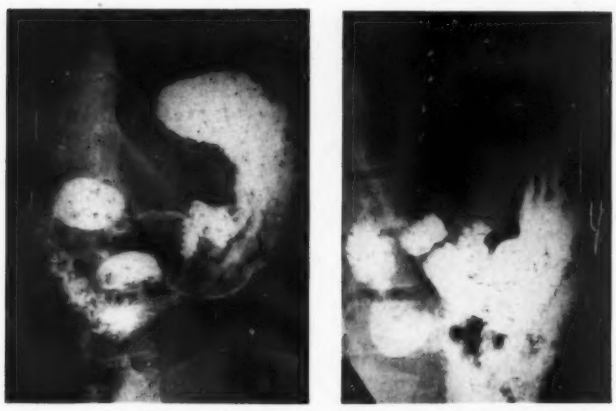
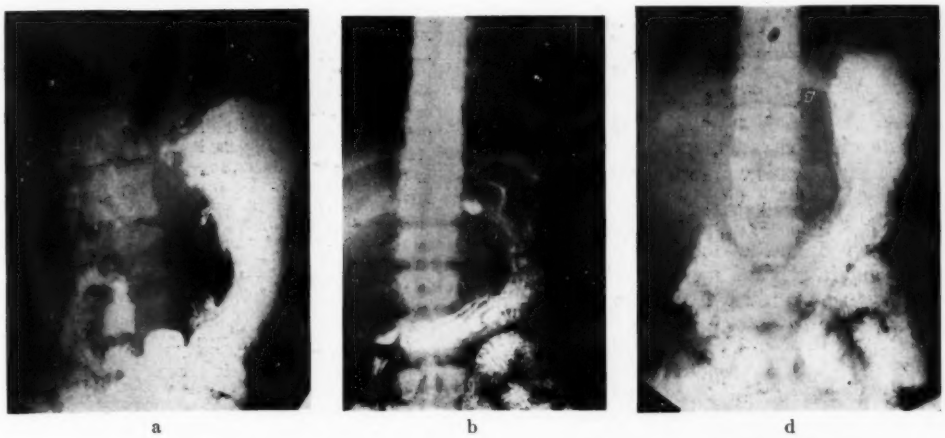


Fig. 4. a, left, Preoperative x-ray film showing diverticulum of the third portion of the duodenum; b, postoperative x-ray film 3 weeks after invagination of the diverticulum (official U. S. Naval photograph).

cult blood. Gastric analysis disclosed normal values for acid and contained no blood or lactic acid. Roentgenograms of the gastrointestinal tract showed no defect in the esophagus or stomach. At the juncture of the second and third portions of the duodenum, there was a large diverticulum measuring 5 centimeters in its widest diameter (Fig. 4). At the end of 4 hours the stomach was empty, but a small residue was seen in the diverticulum, the neck of which appeared directed caudad. Laparotomy through an upper abdominal midline incision under continuous spinal pontocaine anesthesia was performed on May 16, 1945. The stomach and gall bladder were normal. The distal duodenum was visualized by incising the posterior peritoneum, and a large diverticulum was exposed arising from the superior border of the duodenum. Ligation of a single large vessel which coursed over the sac permitted dissection and mobilization of the entire pouch. This was found to communicate with the lumen of the bowel through a well demarcated muscular ring in the bowel wall. The diverticular sac was inverted into the gut through this muscular ring, which was closed by means of interrupted nylon sutures. The posterior peritoneum was reconstructed and the abdominal parietal wound was closed in layers with steel alloy wire. Liquid diet was permitted sparingly immediately after operation. Soft food was begun on the fourth day and a full diet on the seventh postoperative day. The patient was allowed out of bed on the fourth postoperative day. The wound healed *per primam*. There were no complaints referrable to the gastrointestinal tract following the operation. Gastrointestinal x-ray series on June 7, 1945, revealed no evidence of the previously noted diverticulum (Fig. 4). At the end of 4 hours, the stomach was empty and the head of the barium meal was in the cecum. The patient was discharged from the hospital to duty 4 weeks after operation.

CASE 4. F. J. D., a 27 year old veteran, was admitted to the hospital October 16, 1944, with the complaint of pain in the upper abdomen. The pain, of 2 years' duration, was dull, radiated to the upper right quadrant, and was intermittent. For many months, it had wakened him each morning. It had no relationship to meals or to the type of food eaten, and was not relieved by alkalies. Vomiting was not a complaint. The patient had lost 20 pounds during the previous 30 months, although his appetite remained good. Bowels were normal. He smoked 20 cigarettes per day, but did not use alcohol in any form. The patient had received a medical discharge from the Army in October, 1943, because of the diagnosis of diverticulitis. Appendectomy was performed in May, 1944. The family history was not pertinent. Physical examination showed the patient to be a tall, spare young adult male, not appearing ill. His weight was 150 pounds. The particulars of the examination were essentially normal with the exception of the abdomen. No distension or fluid was present. The liver and spleen were not felt and no masses were palpated. Moderate tenderness resulted from deep pressure in the epigastrium, the point of greatest discomfort being just to the right of the midline, 3.5 centimeters below the costal arch. Laboratory findings were normal. Repeated examinations of the stools were negative for ova, parasites, and occult blood. Gastric analysis disclosed normal values for free and total acid. Gall bladder visualization studies showed normal filling and emptying, with no evidence of calculus. Gastrointestinal x-ray series revealed a diverticulum measuring 2 by 1.5 by 1 centimeter, arising from the posterior wall of the stomach near the lesser curvature just below the esophageal hiatus and connected to the stomach by a narrow neck (Fig. 5). The barium remained in the diverticulum for 24 hours (Fig. 5). On November 13, 1944, laparotomy was performed under continuous



a b d

c

Fig. 5. a, Diverticulum near cardiac orifice of the stomach; b, appearance of diverticulum 4 hours after barium meal; c, operative exposure of diverticulum showing ligated vessels; d, postoperative x-ray film 22 days following invagination of the diverticulum (official U. S. Naval photograph).

spinal pontocaine anesthesia, employing an upper midline incision. The lesser bursa was entered through the gastrohepatic omentum, and the posterior gastric wall was mobilized. The diverticulum, about the size of a maraschino cherry, was identified on the posteromesial wall of the stomach directly beneath the cardiac orifice. The neck was 8 millimeters in diameter. A single artery was seen coursing over the pouch (Fig. 5). The sac was inverted through the neck, i.e., through the defect in the gastric muscularis, and the muscular ring closed by means of a continuous Lembert suture of chromic catgut No. 0. Five grams of microcrystalline sulfathiazole suspension were placed in the lesser cavity, and the gastrohepatic ligament was closed. The abdominal incision was closed in layers with steel alloy wire. Nothing was given by mouth until the third postoperative day, when liquid diet was permitted. Soft food was ordered on the fifth day and full diet on the seventh. The patient was ambulatory following the sixth postoperative day. Healing of the wound was uncomplicated, and the patient was discharged from the hospital without complaints 26 days after operation. Gastrointestinal x-ray series on December 5, 1944, disclosed no defect at the diverticulum site.

Case 5. C. S. W., a 25 year old seaman, was admitted to the hospital on May 10, 1945, complaining of epigastric pain and frequency of bowel movements. The epigastric pain appeared after eating and was not relieved by soda or food. The bowel movements numbered 3 to 5 daily, and were often liquid and associated with crampy abdominal pain that appeared to be distinct from the epigastric distress. The patient had lost 18 pounds in the preceding 2 months aboard ship. Physical examination showed a thin young male with definite local tenderness on deep pressure in the upper epigastrium, and some tenderness over the sigmoid area. Gastric analysis was normal. There was a slight anemia. An x-ray examination showed a gastric diverticulum arising near the esophagogastric junction which seemed to project posteriorly and to the left. The diverticulum was still visible at the end of 4 hours. A barium enema showed the loss of haustrations typical of a colitis. Operation on May 21, 1945, under serial spinal anesthesia revealed the diverticulum as shown by x-ray examination. It was treated by invagination and closure of the muscular ring with interrupted silk sutures. The patient made an uneventful recovery from operation and an x-ray examination showed no evidence of the previously present diverticulum. He was relieved of his epigastric distress, but his symptoms of colitis persisted.

These 5 patients with gastric and duodenal diverticula presented vague upper abdominal

symptoms which had persisted for some time in spite of treatment. Usually, the treatment had been given for one of the more common upper abdominal lesions, ulcer, or gall bladder disease. A finding common to the group was the retention of radiopaque material in the diverticulum. This condition was shown to be due to a sac with a very small neck, and it is probable that the symptoms arose from recurring distension of the sac. Repair of the diverticulum by invagination of the thin sac of mucosa produced a relief of symptoms. The invaginated mucosa apparently atrophies or shrinks up to resume a normal position as shown by the normal appearance of the postoperative roentgenograms.

SUMMARY

1. A brief review of the incidence, etiology, symptoms, and diagnosis of diverticula of the upper stomach and duodenum is given.

2. A technique of treatment by invagination of the diverticulum and suture of the muscular ring is described.

3. Five cases are presented in which the patients were treated by this method with relief of symptoms due to the diverticula in all cases.

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GROWTH OF HUMAN TROPHOBLAST IN EYE OF RABBIT
ITS RELATIONSHIP TO THE ORIGIN OF CANCER

A Preliminary Report

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A RELATIONSHIP between the pregnancy trophoblast and cancer has long been suspected (10, 14, 81, 94). It was particularly well explored by John Beard (10, 11, 12, 13) on the basis of extensive embryological and zoological studies (5, 6, 7, 8, 9). It was further implied in the later experimental work of Loeb (55, 56, 57), Brachet, Maximov, Blumenthal and Auler, and Kido. It is the purpose of this communication further to clarify this relationship particularly in the light of vertebrate metagenesis.

Experiments to be described are the first of a series of transplantations of human placental material in the anterior chamber of the eye of the rabbit. They constitute confirmation of similar experiments performed by Kido, and serve to illustrate *in vivo* the results obtained by Maximov with growth of rabbit conceptus in tissue culture.

Our results indicate that heterologous trophoblast grows easily and promptly in the anterior chamber in a manner analogous to malignant tumors.

EXPERIMENTAL MATERIAL AND PROCEDURE

Tissue explants obtained from normal human placentae aged 2, 5, 7 months and at term were placed in the eyes of 8 rabbits including two serial transfers. A total of 27 implants were made in 16 eyes through incisions performed at the corneal-scleral margin under local anesthesia produced by instillation with 5 per cent cocaine hydrochloride. Explants were obtained, after dissecting off the maternal portion, from within and just below the spongy layer of the placenta. A section of the 5 months' placenta is shown in Figure 1. Of the 8 rabbits, which were all less than 4 months old and obtained from widely separate sources, 6 were virgin albino females, 1 was a young albino male, and 1 a black young male. The females were kept in two large cages, the males each in a separate cage, and all were kept in a quiet dark room. The use of different placentae in animals of unlike strains insured against the probability that results might be due to virus infection. Corneal incisions were well healed after several days. A latent period of from 2 to 4 days preceded evidence of growth. All implants were examined every few days with a binocular magnifier (×10).

Rabbit 1. Small albino virgin female (circa 1.5 kgm.) inoculated with 5 months' placental tissue.

Right eye—1 implant 1 by 1 millimeter placed 4 millimeters below corneal-scleral junction. Left eye—1 implant 1 by 1 millimeter close to junction.

7 days: Right eye—Implant 2 by 2 millimeters. Eye hyperemic around edges. Incision site slightly raised. Implant pale yellow and translucent. Left eye—Implant not well demarcated. Zone of diffuse growth 2 by 3 millimeters. Cornea vascularized between implant and sclera.

26 days: Right eye—Implant 2 by 3 millimeters. Appears to have moved closer to sclera. Left eye—Implant 4 by 4 millimeters and round. Well demarcated, yellowish, no diffuse zone. Upper border of vascularized implant attached at corneal-scleral junction.

80 days: Right eye—Implant has all but disappeared. Very small mass remaining at corneal-scleral margin. Left eye—Implant almost circular, yellowish with a more diffuse but well demarcated crescentic area extending beyond the denser yellowish mass. Appears to be growing within or attached to the cornea and is well vascularized. Eye slightly opalescent with granular area below entire implant, but otherwise normal in appearance. Little change in size.

Rabbit 2. Medium size (circa 2 kgm.) albino virgin female inoculated with 5 months' placental tissue.

Right eye—Three implants measuring about 1 by 1 millimeter were placed 2 to 3 millimeters from

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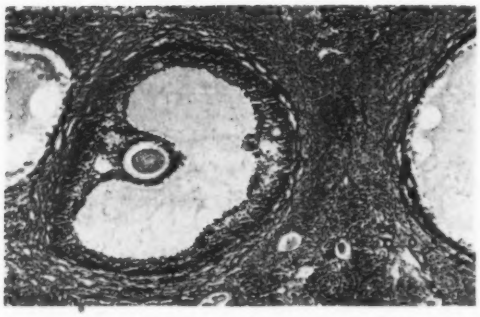

Fig. 1. Ripening follicle in left ovary of Rabbit 2. It is seen in the middle of the same ovary shown in Figure 2. ×65.

junction at 12, 6, and 8 o'clock. Left eye—One implant 2 by 1 millimeter at junction and at 11 o'clock; second implant 1 by 1 millimeter at 3 o'clock 2 millimeters away from junction.

7 days: Right eye—Densely clouded and glaucomatous; but implants visible. Only 12 o'clock implant growing and is now 2.5 by 2 millimeters. Situated 2 millimeters below junction it appears very close to the iris. Left eye—11 o'clock implant pale yellow and lobulated. No diffuse zone, no glaucoma, size 1.5 by 2 millimeters. Three o'clock implant 2 by 1 millimeter, pale pink, not attached.

18 days: Right eye—No further growth of 12 o'clock implant, no change in appearance. When this growth was sectioned it was found to constitute a very thickened portion of the iris outside of which no discrete mass was found. Since this implant was seen from the beginning at a point near the iris and appeared later to have grown very close to the iris, invasion of the iris may have occurred during observations. Histological section of the remaining right eye implant (Figs. 5, 7, 8, and 9) shows the presence of giant cells and syncytial masses strongly

Fig. 3. Ripening follicle in ovary of Friedman doe injected with urine obtained from black male Rabbit 3. ×65.

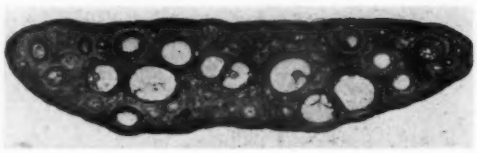

Fig. 2. Left ovary of Rabbit 2 showing cystic enlargement of follicles. ×10.

suggestive of chorionic villi. The other two implants had apparently been absorbed. Left eye—11 o'clock implant 2 by 3 millimeters, fixed to cornea which was herniated at site of growth and appeared like a small boil (Fig. 4*a*). Three o'clock growth unchanged (Fig. 4*b*). Eye glaucomatous but clear.

This animal was killed after the eyes were removed under general anesthesia. When the herniated implant of the left eye was accidently touched with forceps it broke open at one point. The intraocular pressure produced a fine stream of aqueous humor 18 inches high.

When the abdomen was opened the uterus was found definitely hyperemic. The ovaries showed no gross changes. The eyes, uterus, and ovaries were removed and fixed in Bouin's fluid, sectioned, and stained. The stained section of the uterus shows proliferation of the labyrinthine glands brought about by steroid hormones, while the ovaries show follicle ripening and a beginning of the formation of follicular cysts (Figs. 1 and 2).

The stained section of the 11 o'clock implant of the left eye is shown in Figure 4*a*. There is much distortion of the iris and bridges connecting the iris with a hypertrophied ciliary body. The herniation was followed also by marked distortion of the iris, which

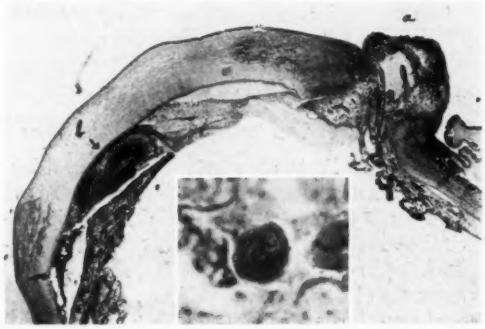

Fig. 4. Section of anterior chamber of Rabbit 2. Lack of herniation at site of degenerating implant *b* may indicate that extrusion of *a* is in part due to erosion by growing trophoblast whose morphology may be obscured by somatic response of iris and ciliary body. Left eye. ×10.

Fig. 5, inset. Giant cell *a* in Figure 7 photographed through a dark green filter. The nuclei arranged at the periphery give this cell the appearance of a chorionic villus. ×200.

Fig. 6. Section of normal 5 months' placenta. Compare syncytium with that to be seen in both Figures 8 and 9. ×200.

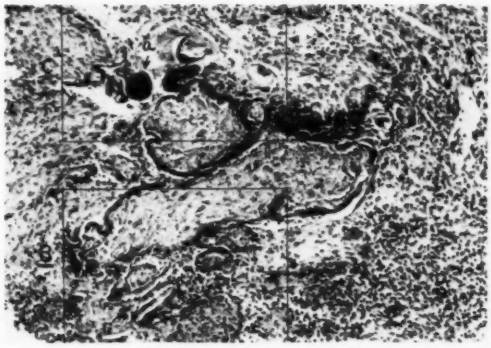

Fig. 7. Section of iris from right eye of Rabbit 2. Giant cells, whorls, and syncytial masses suggest chorionic villi. ×90. Photographed with light green filter.

was pushed up against the cornea. Part *b* in Figure 4 shows the second implant to be degenerating.

Rabbit 3. Medium size black young male (circa 2 kgm.) inoculated with 5 months' placental tissue.

Right eye—Implant 2 by 1 millimeter near corneal-scleral margin. Left eye—Two implants, one near margin 2 by 2 millimeters, the other 2 by 2 millimeters was pushed to the bottom of the anterior chamber.

7 days: Right eye— 3 by 1.5 millimeters, pale yellow and well demarcated. Surrounded by clear zone less than 1 millimeter wide. Beyond zone a dense white outer margin was seen about 1 millimeter wide. Very small knob on lower margin of implant. Slightly diffuse zone extending to 3 millimeters around growth. Incision site elevated. Sclera hyperemic for a distance of 8 millimeters on each side. Implant appears attached near incision site. Left eye—Implant near junction 3 by 3 millimeters. Bottom implant 2 by 5 millimeters. Chamber slightly cloudy and glaucomatous. Sclera markedly hyperemic near first implant close to incision site. This implant has a small knob protruding from lower border. It is well demarcated and yellowish. Lower implant has ragged edges and is rectangular with well defined but diffuse brush-like extensions from each end. They have the appearance of strands characteristic of sarcomas cultured *in vitro*. The ragged edges of the growth examined through the cornea with a Greenough type binocular microscope (×40) showed growing sheets of tissue which appeared like a surface of wave-like crests, finely granular with a beautiful opalescent sheen, showing well against the black background. In contrast to the brush-like extensions on the ends of the growth the sheet-like proliferation from the same implant is reminiscent of carcinoma.

26 days: Right eye—Implant 3 by 6 millimeters. Oval in shape and yellowish with well demarcated crescentic diffuse extension on the left side toward

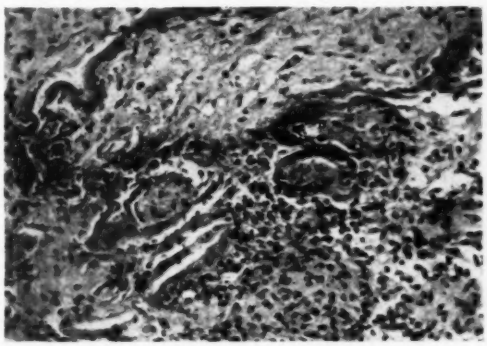

Fig. 8. Higher magnification of part *B* outlined in Figure 7. Photographed with dark green filter. The rows of nuclei in the syncytial strands and whorls can be readily seen. ×200.

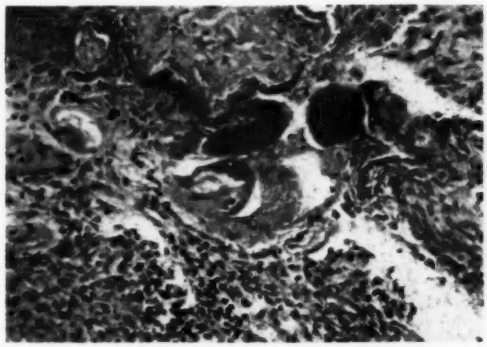

Fig. 9. Higher magnification of part *C* outlined in Figure 7. Photographed with dark green filter. The giant cell mass in the center appears to be arising out of a chorionic villus. ×200.

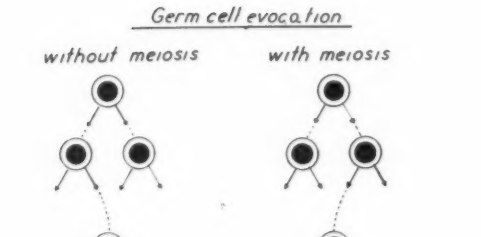

Fig. 10. Diagrammatic chart of germ cell development. Normal evocation on the left. Evocation culminating in cancer is shown on the right. The dotted lines indicate phases of simple mitotic multiplication and only one of the resulting cells is figured to indicate subsequent development which represents the fate of that single cell.

inner canthus. Left eye—Top implant 3 by 5 millimeters. Bottom implant circa 2 by 5 millimeters. Top implant appears attached of the cornea and sclera. No cloudiness. Growth vascularized and spreading down in the direction of the inner canthus where a diffuse zone is visible about 3 by 3 millimeters. Bottom implant also yellow and vascularized. Brush ends have now almost disappeared but implant is slightly larger.

80 days: Right eye—Implant 4 by 6 millimeters, vascular. Nictitating membrane appears large but normal in color. Left eye—Upper implant 4 by 7 millimeters, vascularized. Bottom implant 3 by 10 millimeters, crescent shaped. Eye slightly glaucomatous and clear. The urine from this male rabbit was collected on the twenty-first day and injected into a Friedman doe. At the end of 48 hours the reaction was positive for the presence of chorionic gonadotropin although as a pregnancy test it would have been rated as doubtful since there were seven blood points observed instead of frankly hemorrhagic follicles. However we are here dealing with the urine of a male rabbit rather than from that of a pregnant woman. The ovaries were removed and prepared for histologic examination. A section is shown in Figure 3.

Rabbit 4. Large albino male (circa 3 kgm.) inoculated with 5 months' placental tissue.

Right eye—One implant 1 by 1 millimeter near corneal-scleral junction. Left eye—Three implants, all 1 by 1 millimeter. One near junction at 12 o'clock, two implants at 4 o'clock placed between pupil and junction.

7 days: Right eye—Implant now 2 by 2 millimeters. No glaucoma. No inflammation. Eye clear. Left eye—Very cloudy containing an irregular broken ring of yellowish implants in and below pupil. Glaucomatous. No apparent inflammation.

26 days: Right eye—Well vascularized implant 5 by 4 millimeters. Eye glaucomatous and clear. Left eye—Cloudy, difficult to observe. Animal in apparent distress. Very restless and inclining head to one side. Occasionally squeals as if in pain. Implant appears as large irregular broken mass situated mostly near bottom of chamber. No apparent inflammation.

50 days: Right eye photographed (Fig. 11). Left eye too cloudy. Not photographed. Right eye implant 6 by 4 millimeters. On the fifty-first day animal anesthetized with sodium pentobarbital and left eye was removed, fixed in Bouin's fluid, sectioned and stained. Implant in right eye was firmly attached to the cornea of which a piece 7 by 5 millimeters was excised. Two fragments were cut from this piece and transplanted, along with the attached cornea from which implant could not be separated,

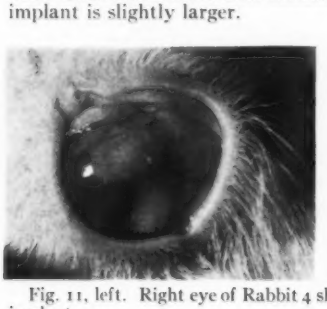

Fig. 11, left. Right eye of Rabbit 4 showing vascularized implant.

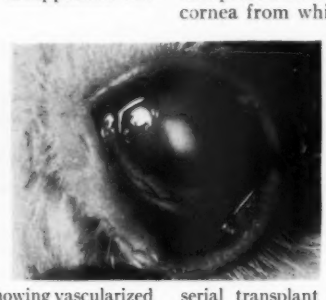

Fig. 12, center. Right eye of Rabbit 4a bearing serial transplant obtained from right eye of Rabbit 4.

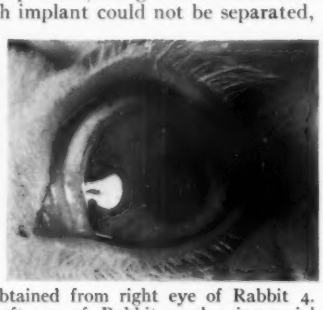

Fig. 13, right. Left eye of Rabbit 4a bearing serial transplant obtained from right eye of Rabbit 4.

into a small, young albino female virgin rabbit (Rabbit 4a). The testes from the host rabbit were removed, fixed, sectioned, and stained. There was indication of some inhibition of spermiogenesis. A histological section of the left eye shows the iris and ciliary bodies to have hypertrophied markedly and grown entirely across the anterior chamber. Both iris and ciliary bodies are connected by many long bridges. Although the normal rabbit eye may show a remarkably large ciliary body and outgrowths of loose vascular tissue from the iris the eye of Rabbit 4 represented a very marked departure from the normal and after 60 days there were no signs of inflammation.

Rabbit 4a. Young albino virgin female (circa 1.5 kgm.) implanted with corneal fragments obtained from Rabbit 4.

Right eye—Implant 2 by 2 millimeters including cornea. Left eye—Implant 1 by 3 millimeters including cornea. Within 24 hours growth was apparent. Within 3 days right eye transplant measured 3 by 4 millimeters. Left eye implant 2 by 3 millimeters. Right eye markedly inflamed (Fig. 12). Left eye normal (Fig. 13).

30 days: Right eye—Implant growing attached to the cornea. Size 2 by 8 millimeters, vascularized. Left eye—Implant now 2 by 5 millimeters. At first irregular it now appears more like the right eye implant.

Rabbit 5. Small albino virgin female (circa 1.5 kgm.) inoculated with tissue from a 7 months' placenta.

Right and left eye—One implant in each, 2 by 1 millimeter near corneal-scleral junction. Grew slowly after about 4 days.

30 days: Both implants now 2 by 2 millimeters.

68 days: Both implants 1 by 1 millimeter. Definite regression has occurred after a very slow initial growth.

Rabbit 6. Medium size albino virgin female (circa 2 kgm.) inoculated with tissue from a term placenta. Organ was soft, spongy, and very bloody.

Right eye—Two implants 2 by 2 millimeters. One in area of pupil, the other at the corneal-scleral junction. There was a latent period of growth of about 12 days. Left eye—Three implants, all near pupil around the edge. Size 2 by 2 millimeters.

27 days: Right eye—Pupil implant almost entirely absorbed. Implant at junction well demarcated, yellow. Size 2 by 5 millimeters. Left eye—All 3 implants absorbed.

32 days: Right eye—Implant 3 by 5 millimeters. Slightly vascularized.[1]

Rabbit 7. Small albino virgin female (circa 1.5 kgm.) inoculated with 2 months' placental tissue.

Right eye—Two implants 2 by 2 millimeters placed at 4 millimeters below corneal-scleral junction. Left eye—Two extremely small implants placed 4 millimeters below junction at 12 o'clock.

All 4 implants grew only slightly. After 38 days 2 implants were left measuring about 1 by 1 millimeter. They appeared not to be growing.

The experiments herein described indicate that normal human pregnancy trophoblast, when grown in the anterior chamber of the eyes of rabbits, behaves like a malignant tumor grown in a similar medium. This raises the question of how closely related these two tissues are. Our experiments, as well as a great many other data, suggest that all malignant tumors regardless of their protean character, are fundamentally trophoblastic. Admittedly, if this is true there are many things to be explained; and in the case of most tumors the relationship between pregnancy and cancer trophoblast can only be a subtle one. We know that trophoblast *per se* can be violently malignant; indeed its malignancy can be of a degree not exceeded by any known tumor. That trophoblast, like other tissues, may be capable of undergoing malignant degeneration cannot be seriously considered here because no one knows what malignant degeneration is. Moreover, it is particularly because of the need to explain "malignant degeneration" that the relationship between trophoblast and cancer is being examined. Also if we keep in mind that growth of the implanted heterologous trophoblast in the anterior chamber was observable grossly only a few days after inoculation it is very doubtful if it can be said to have undergone "malignant degeneration."

The analogous behavior of trophoblast and malignant tumor implants is consistent with the generally accepted observation that chorionepithelioma appears as a simple overgrowth of normal trophoblast cells (22).

If cancer is fundamentally trophoblastic it can only be germinal in origin. It is well to point out the semantic limitation of the term cancer as applied to a complex structure whose malignant properties are attributable to one component only, for if cancer is trophoblastic it is, like the chorion, a dual tissue unless it happens to be anaplastic. In this case it might qualify as a polymorphic manifestation of chorionepithelioma. The nontrophoblastic component of the chorion is embryonic whereas the nontrophoblastic component of cancer

[1]The presence of syncytial steroids was verified in the implants of this animal by histochemical methods. Private communication from G. B. Wislocki.

is somatic. In either case the embryonic or somatic components tend to limit the relative growth of the trophoblast. Indeed the growth of the former would appear to be stimulated by trophoblast. This is particularly suggested by the marked growth of embryonic mesenchyme pushing the pregnancy trophoblast, at first relatively smooth, into the multibranched chorion frondosum eventually. Thus the relative development of each tissue gives the combination its own particular architecture.

Because of its antagonism to somatic tissues (embryonic as well as adult) trophoblast cannot be described as embryonic. To the contrary, trophoblast precedes the embryo in development and represents the asexual or preembryonic generation. Better known in the invertebrates the asexual generation is generally recognizable as the trochophore, or some modification of it, the morphology of which is practically identical through six different phyla.

Both the asexual (trophoblast) and the embryonic (sexual) generations stem from a single origin: a diploid totipotent cell (germ cell). Germ cells are totipotent because they can give rise to complete embryos. If a diploid totipotent cell undergoes meiosis a gamete-like cell is formed. If the diploid totipotent cell proliferates as such (without meiosis), more germ cells are formed, one or more of which may eventually proceed through differentiation to definitive embryogenesis.

Diploid totipotent cells have three possible fates. They may: (1) proliferate through simple mitosis and produce more totipotent cells, or (2) proliferate through meiosis and produce gamete-like cells, or (3) proliferate through differentiation and produce embryos.

During the early cleavage of activated gamete-like cells some of the daughter cells are trophoblast and the remainder are totipotent cells. Thus in *1* all resulting cells are totipotent. As a result of *2* and after activation, only some of the cells are totipotent. In *3* all resulting cells lose their totipotence but all cells do not *totally* lose their potencies.

A gamete-like cell, after activation or fertilization, divides to produce trophoblast cells (asexual generation) and embryo-forming cells. The latter represent totipotent cells, one or more of which differentiates in the process of definitive embryogenesis while the remaining diploid totipotent cells, the total potency of which is reserved from early cleavage, comprise the germinal stream. During gestation the embryo is formed by the direct differentiation (without meiosis) of a totipotent cell (germ cell) segregated from the trophoblast during very early cleavage. In mammalian eggs, as in the eggs of a number of lower forms, the segregation most likely occurs at the very first cell division (75). So far as totipotency is concerned the germ cell *per se* can give rise to the sexual generation only. After meiosis, however, a resulting gamete-like cell can give rise during cleavage both to the trophoblast (asexual generation) and to embryo-forming diploid totipotent or germ cells (Fig. 10).

The two generations develop in autonomy of each other as reflected in their eventual mutual antagonism. The relationship between the asexual and sexual generations is the basis for metagenesis.

Metagenesis, sometimes referred to as alternations of generations, implies a discontinuity in the life-cycle whereby in animals the definitive sexual generation may be said to be preceded by a nonembryonic asexual generation. There may be overlapping and the discontinuity is not absolute. Hitherto regarded in the higher animals as a more or less academic concept, metagenesis assumes a fundamental importance with regard to the etiology of cancer.

Like other developmental phenomena cancer is the result of organizer action upon competent cells—specifically totipotent or toticompetent cells (59, 89). The conclusion that cancer cannot develop from cells of lower potency is based upon accepted morphogenetic principles (89, 66). Organizer stimuli upon totipotent cells, as well as cells of lower potency possessing fewer competences, may be mediated by hormones, hydrocarbons or viruses. The diploid totipotent cells of higher animals are normally dispersed throughout the soma (sexual generation) (4, 11, 21, 61, 70, 74, 84). This dispersion has substantial phylogenetic roots, since these cells are responsible for complete regeneration in lower forms (17). Their early separation from the trophoblast of the conceptus is apparent at the four-cell stage

in a number of mammals (49, 85). From then on the trophoblast cells and the totipotent (embryo-forming) cells go their separate way, "the one can never become the other" (85).

The somatically dispersed totipotent cells, in contrast to embryonic somatic cells of lesser potency do not take part in repair processes and indeed are normally functionless in the higher chordates (45, 94). Their total potency or competence is reserved since early cleavage (78) and is not acquired from somatic cells (92), whose lower order potency or competence cannot give rise to cells of higher potency (2, 18, 32, 67). This principle of the irreversibility of potency has been well expressed in connection with evolution and is known as Dollo's dictum. It states that so far as animal structure is concerned evolution is irreversible; but regarding adaptation to a new environment simulating conditions which obtained in the past in another environment, evolution is reversible. In this case new organs may be developed from reserved *anlage*, the new organs serving functions analogous to old organs which have disappeared never to return (29). This generalization applies with equal force to cellular development. Phylogenetically and ontogenetically cellular potencies once lost or expended can never be regained. This is not to be confused with the various possible fates of pluripotent cells which have a number of prospective potencies. For example undifferentiated mesenchymal cells may differentiate into hemocytoblasts, macrophages, primitive fibroblasts, osteoblasts, chondroblasts or several other forms. Some of these products of mesenchymal differentiation may likewise have a number of prospective potencies. Existing confusion in terminology may make it appear that certain differentiated cells may give rise to more primitive cells. But it was eventually verified that there is no going back on the scale of potencies (2). It is as impossible for totipotent cells, for example, to arise from somatic cells as it would be for a neuron to form primitive ectoderm or for an erythroblast to form primitive mesenchyme. As for mutations, so far as they may be said to have any bearing on potency they can only be followed by an overall decrease rather than an increase as it is apparent on the evolution scale (18). With respect to ontogenesis the concept of gene-mutations as they are known to occur would appear to be quite irrelevant.

From the number of somatically dispersed totipotent cells counted in 4.5 millimeter embryos (45), and in a number of elasmobranch embryos of various ages (7, 8, 9), it can be calculated that there are at least 3×10^8 totipotent cells—possibly more—dispersed in adult man, an average of 2 for every cubic millimeter of tissue. This is after making allowance for 50 per cent degeneration and assuming that these cells continue to proliferate at the same rate as their surrounding cells, as they are known to do in embryos (8). These cells possess a competence for either trophogenesis or somatogenesis (embryogenesis) (Fig. 10). The latter occurs only by differentiation (without meiosis) of a germ cell and possibly only within a trophoblastic medium (decidua). Trophogenesis, on the other hand, can occur only after a germ cell or totipotent cell has undergone meiosis (heterotypic mitosis) resulting in a gamete or gamete-like cell which, now obliged to divide or perish, possesses an obligative competence for trophogenesis. The occurrence of teratomas in practically every part of the organism, as well as the occurrence of extragenital chorionepitheliomas in both sexes, is further evidence for the existence of somatically dispersed totipotent cells, which although they usually remain functionless may unfortunately be stimulated to attempt a new life-cycle. Moreover considerable evidence exists for the occurrence of ectopic meiosis (heterotypic mitosis) (4, 35, 74, 89, 90, 94).

Direct evocation of more than one embryopotent or diploid totipotent cell within a *single* trophoblastic blastocyst results in twinning (polyembryony) to which metagenesis is a necessary corollary (51, 68, 76, 83). Benign teratomas (ectopic sexual generation) in the young are most likely identical twins evoked at the same time as their host (72). Identical twins are examples of polyembryony in man. Malignant teratomas (malignant ectopic conceptuses) consist of more or less distorted or enmeshed embryonic tissue, of a genetic composition different from that of their host (change in genetic composition produced by

meiosis) (61), occurring in a trophoblastic matrix or apposed to it, which matrix has arisen through the activation of a gamete-like cell developed through meiosis from a diploid totipotent cell.

The malignant character of trophoblast has been demonstrated by *in vitro* culture of definitive rabbit embryonic tissue in the presence of its own trophoblast unavoidably introduced with the embryonic tissue (63). In culture the cytotrophoblast infiltrates, erodes, and completely destroys the embryonic tissue (63). Recognized in these experiments as due to release of the trophoblast from the somatic restraint exerted by the entire embryo and mother these results constitute confirmation of previous observations (23). The occasional striking resemblance of phenomena observed in these experiments to chorionepithelioma (63) indicates that trophoblast can exhibit its violently malignant properties with or without assuming the appearance of chorionepithelioma. Because it consists of almost pure trophoblast (cytotrophoblast and syncytium) chorionepithelioma is one of the most malignant forms of cancer. Normally the trophoblast is prevented from overgrowing as chorionepithelioma by a humorally mediated factor produced by the embryo and mother. The question of its identity will be discussed elsewhere.

The occurrence of chorionepithelioma in males, primary in the liver (65), primary in the brain (84), primary in the mediastinum (46, 47, 52), metastasizing as adenocarcinoma or sarcoma (1, 62), and grading by extension into carcinoma or sarcoma (35, 82) likewise constitutes evidence not only for the malignant character of trophoblast in the relative absence of its physiological inhibitor normally produced by an embryo and mother (20, 63) or male host; but at the same time for the existence of somatically dispersed totipotent cells and for somatic response which endows trophoblast with the appearance of carcinoma or sarcoma.

In those malignant teratomas in which the trophoblast is clearly separate from the remainder of the teratoma, it is the trophoblast alone which is responsible for any metastases (37). Destruction of embryonic tissue by trophoblast has been observed in ovarian teratomas in guinea pigs (55) and confirmed repeatedly (3, 24, 27, 56, 57, 58). Significantly, testicular chorionepithelioma or primary chorionepithelioma in the mediastinum or in the brain is identical with primary uterine chorionepithelioma. Since the testes contain a high concentration of totipotent cells normally canalized, it is not surprising that occasionally (following meiosis) one becomes activated, before spermiogenesis occurs, to form ectopic trophoblast, exhibited in some cases as chorionepithelioma, in others as carcinoma or sarcoma. It is also significant that even the primary carcinomas and sarcomas occurring in testes are known to produce chorionic gonadotropin.

If the trophoblast cell and the cancer cell are one, the normal trophoblast of pregnancy should be indistinguishable from cancer in some cases at least. By the fresh tissue technique (38) the trophoblast is found to be the only cell indistinguishable from cancer. Moreover in the trophoblastic portion of the cultured rabbit conceptus, the presence was noted of practically all cell types known to be malignant (63). The observation, in a large series of autopsies of pregnant women, that metastases or dispersion of normal pregnancy trophoblast may be found in over 80 per cent of the cases is further confirmation of the malignant character of trophoblast (50, 79, 87). Furthermore when not a part of the normal conceptus of pregnancy, trophoblast cells have never been observed except as cancer (1).

Heterologous malignant tumors may be successfully transplanted into the anterior chamber of the eyes of animals (40, 41, 42, 43), whereas attempts to grow heterologous late embryonic and adult somatic tissues have failed. Yet heterologous late trophoblast (term placenta) will grow (53). Therefore heterologous transplantability as a criterion of malignancy is fulfilled by trophoblast.

The human placenta has a somewhat higher rate of aerobic glycolysis than nonplacental tissues. This is not in itself very significant; but when the cytotrophoblast and syncytium are peeled from the placenta the ablated trophoblast (chorion) exhibits a high aerobic glycolytic index whereas the residual placenta now

shows the same value as normal somatic tissues (16).

As shown previously the pregnancy trophoblast is the only "normal" tissue known regularly to metastasize (50, 79, 87). Finally the trophoblast of pregnancy has been observed without any embryo at all, the latter being destroyed at an early stage. In such cases the trophoblast often continues to erode and infiltrate the host. The distinction between such cases and chorionepithelioma is arbitrary (20, 69, 95).

Morphological multiplicity of malignant tumors is in part a function of the type of tissue in which the ectopic trophoblast develops and of the degree of somatic reactivity or host response manifested by the surrounding cellular elements. This response is fundamentally the same as that which is responsible during gestation for chorion formation and placentation. The combination and relative concentration of trophoblastic and somatic cells determine the architecture and malignancy of each type of malignant tumor. Thus the higher the concentration of trophoblast the higher the malignancy. An anaplastic tumor is one in which the concentration of trophoblast approaches 100 per cent because the relative lack of host response has resulted in little or no investment of the trophoblast by the somatic elements in the vicinity. At the same time the somatic architecture has not been impressed upon the trophoblast. Whereas in pregnancy the chorion is formed following the somatic tissue response of the embryo and mother to the trophoblast, cancer is formed by the tissue response of the postembryonic soma to an *ectopic* trophoblast.

Somatic response or tissue reactivity forms an extremely complex chapter of morphogenesis; and is related to growth stimuli, differentiation and variations in cell form. Variations in cell form in cancer are well known and have been previously described for trophoblast (63). The anaplasia and polymorphism characteristic of Jensen sarcoma when grown *in vitro* are greatly modified in the presence of somatic tissue when the tumor is transplanted *in vivo* (28). A Flexner-Jobling tumor transplanted into the rat endometrium produced a decidual reaction (64), resulting in a malignant decidu-oma paralleling placentation. When rabbit tumors are transplanted into the eyes of alien species variations in parenchymal-stromal relations may occur (40). The heterologous transplantation of human carcinomas under similar conditions may be followed by marked histological changes (41). A rabbit squamous cell carcinoma varied histologically according to the tissue into which it was transplanted (43). Chorionepithelioma may grade into sarcoma or carcinoma (34, 81) or metastasize into either (1, 62). Moreover the reverse process may take place. Trophoblast syncytium has been observed in cancer of the tongue, carcinoma of the breast, sarcoma of the ovary, and of course in testicular as well as in uterine chorionepithelioma and in other carcinoma sections (15). It has also been observed that liver metastases from such diverse tumors as mammary cancer, hypernephroma and chorionepithelioma may be indistinguishable (33). Somatic response is entirely consistent with the observation that the more nearly a malignant tumor approaches the morphology of the tissue in which it grows the less malignant it is.

Somatic tissue response is well illustrated in cancer of the endocrine glands, in which hormone production is associated with the malignant tumor. Cancer of the thyroid for example, unless anaplastic, is composed of trophoblast as well as the hormone-secreting cells. These somatic cells are responsible for reproduction, in a metastatic lesion, of the architecture of the primary growth. Insofar as metastases, or transplants, still contain somatic glandular thyroid tissue, to this extent will such a secondary growth continue to produce thyroid hormone. Metastases or transplants from a primary growth which contains a relatively high concentration of trophoblast cells may be anaplastic thus giving no clue to the primary site. In general, cancer of glandular tissues will not go through many transplants and still produce their characteristic secretions. Cancer of the adrenals, ovaries, and testes are exceptions. These tumors can be transplanted quite a number of times and still produce hormones. Eventually hormone production may cease owing to the destruction of the somatic secreting cells by the cancer cells. The transport or "metastasis" of somatic tis-

sue *per se* is well known although rare. It has been reported for benign hyperplasias. Such "metastases" are simple autotransplants or autogenous grafts. That they may be transported along with trophoblast is to be expected.

When somatic response or the lack of it results in the rare extragenital chorionepitheliomas, or in other highly "cellular" cancers, a strongly positive Aschheim-Zondek reaction may result. Since only the cytotrophoblast produces gonadotropic hormone (96), growths containing a high concentration of cytotrophoblast will produce a pregnancy reaction. Syncytial trophoblast, an adaptation through differentiation of cytotrophoblast to somatic tissue, produces no gonadotropin (96) but sterols instead which are similar to the sex hormones (27, 77, 96). Syncytial adaptation probably accounts in most cancers for an absence of the pregnancy reaction when performed in the usual manner. However, if urine extracts, from persons suffering from cancer, are injected parenterally in immature white rats, growth of the endometrium or enlargement of the prostate has been reported to take place after 24 hours (27, 77). The urine of nonpregnant cows suffering from carcinoma of the eyes without involvement of the genital organs produces follicle-ripening in infantile rabbits (88). This occurs in spite of the fact that pregnant cows give negative Friedman-reactions (88). In testicular chorionepithelioma, in addition to very high prolan titers, gynecomastia, lactation, morning sickness and pregnancy changes in the hypophysis have been reported (26, 39, 48). In fact practically all testicular cancers produce prolan, the titer of which is proportional to the histologic similarity of the tumor to chorionepithelioma (36).

It has been reported that the vitamin uniformity of malignant tumors, regardless of tissue origins, manner of induction, sites and animal species, is such as to indicate that cancer forms in effect a common tissue type (73). It has also been pointed out that the metabolic quotients of a wide variety of tumors are nearly the same; that the lactic acid and sugar contents of sarcoma and carcinoma are approximately the same; that enzyme uniformity among tumors is greater than among the same organs in different animals of the same species; that cytochrome-oxidase activity of a number of tumors is very similar; that in general tumors resemble each other metabolically more than they do normal tissues, or than normal tissues resemble each other (44). It is to be expected that pregnancy trophoblast shares this uniformity with malignant tumors particularly if they are anaplastic.

The life cycle of antithetic metagenesis is indispensable to an understanding of cancer. Metagenesis explains why trophoblast cannot be embryonic. It explains cancer as an antithesis between two fundamental types of tissues occurring normally in every life cycle: trophoblastic (asexual generation) and somatic (sexual generation) (10, 12). Moreover if cancer is trophoblastic it is clear that it cannot arise from any of the primary germ layers of the embryo (71).

In arthropods and vertebrates where the asexual and sexual generations remain long in intimate contact metagenesis is distinctly antithetic. In most other forms the definitive two generations develop on the whole without retaining or developing the same close intimacy. As a result pronounced antithesis is generally not observed. It is to be expected, therefore, that cancer will occur most frequently in arthropods and vertebrates (31, 93).

In Sauropsida and Ichthyosida, the analogue of the trophoblast is the extraembryonic blastoderm (60, 80). With failure of evocation of an embryopotent cell in Sauropsida, the extraembryonic blastoderm proliferates to form a mass of undifferentiated cells called an anidian (60, 66, 85), a result most likely due to the absence of the primary organizer (66). The cancerous quality of this curious growth has been recognized (85). It is reminiscent of the human trophoblast growing without any embryo (20). In animals, as the sexual generation (embryo) gains ascendency over the asexual generation (trophoblast) after the critical period during gestation (or incubation) the trophoblast normally degenerates (6). In other words each individual in the course of its life cycle normally destroys the counterpart of cancer.

The development of an ectopic (normally dispersed) totipotent cell into trophoblast rep-

resents an escape from an individuation field in the host through meiotic mitosis. This is the result of the organizer effect of endogenous (54) or exogenous carcinogens raised usually through the localizing effect of a persistent inflammatory process (30), which may be limited to an exceedingly small area, to a level of concentration required for the gradual escape of a totipotent cell from the individuation field. The resulting ectopic meiosis, cleavage and formation of trophoblast constitute carcinogenesis. An unsuccessful repetition of the metagenetic life cycle results (10, 11). Almost invariably no adequate embryogenesis follows ectopic trophogenesis and the antithesis of the host alone being insufficient, probably through a lack of an internally secreted inhibitor of trophoblast the latter maintains its escape from the individuation field. The soma unable to destroy the ectopic trophoblast invests it if possible, thus producing a characteristic more or less malignant tumor.

SUMMARY OF EXPERIMENTS

1. Normal human trophoblast grows readily in the anterior chamber of the eye of the rabbit and is serially transplantable.

2. It produces chorionic gonadotropin as demonstrated by action on the ovaries of the host and those of a Friedman doe by urine obtained from a transplant bearing male animal.

3. It also produces syncytial sterol hormones as demonstrated upon the uterus of the host and by some degree of inhibition of spermiogenesis in a male host after 60 days.

4. In addition to inflammatory infiltration the presence of giant cells, whirls and strands of syncytium in the iris are suggestive of chorionic invasion.

5. Growth and hormone production of transplanted heterologous trophoblast is now shown in male as well as female animals.

6. This work is being continued.

SUMMARY OF DISCUSSION

Cancer appears to be trophoblastic and develops according to the following sequence:

1. Persistent inflammation associated with high blood titer of carcinogens.

2. Localization and concentration of carcinogenic substances at inflammation site.

3. Meiosis of an ectopic diploid totipotent cell.

4. Formation of a gamete-like cell.

5. Activation and cleavage of the gamete-like cell is followed with formation of trophoblast.

6. Characteristic malignant neoplasm produced by the somatic response of the tissue where trophogenesis has taken place.

7. Maintenance and growth of tumor because of the lack of a humorally mediated inhibitor of trophoblast.

8. In primary uterine chorionepithelioma factors 1 to 5 are absent or modified by the presence of the trophoblast of the pregnancy conceptus.

9. The affinity of viruses for specific tissues brings about their own localization without a necessary previous inflammation which in fact may characterize the first stages of their invasion.

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THE BLOOD SUPPLY OF THE KIDNEY, SUPRARENAL GLAND, AND ASSOCIATED STRUCTURES

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IN a comprehensive study of the blood vessels in the dorsal portion of the trunk, the authors have been impressed by the degree to which the kidneys constitute the core, as it were, of a somatic and visceral assemblage of vascular channels.

Because the renal and suprarenal vessels are, developmentally, parts of a richly plexiform network of channels, adult variation in their arrangement is to be expected. Yet, despite variety, certain arrangements are recurrent. It is the purpose of the present account to: (1) describe briefly certain of the anatomic types, (2) to suggest some practical applications of the morphological observations.

MATERIAL AND METHODS

To date, in this investigation, approximately 400 cadavers have been studied. The figures used in this article were selected from a larger number in the author's collection. Each represents an actual dissection, and portrays a feature, or combination of features, serviceable to the current discussion—but hitherto unrecorded, or disregarded, little emphasized or inadequately described. The field for illustration, in every instance, is limited; overlying structures have been removed, reflected or rolled aside to reveal deeper vessels.

In Figures 3, 4, 7, 8, 11, and 15, the aorta has been totally removed; in Figures 5 and 6 it has been cut and retracted, in Figure 9 a segment of it has been excised, in Figure 14 the vessel remains only at the distal end. In Figure 1 the veins have been wholly removed. In Figure 11 the left kidney has been rolled, on its pedicle, toward the right side. In Figure 12 the psoas major muscle is still *in situ*, in Figure 14 it has been dissected away. In several figures the suprarenal gland has been excised. Specimen in Figure 14 is a case of pelvic kidney described earlier by Anson, Pick, and Cauldwell[1]; the renal vein is, therefore, a tributary of the iliac. In Figure 15 all viscera, the diaphragm, peritoneum, subserous tissue and parietal fascia have been removed; the trunk has been transected to show musculature, etc., the contents of the vertebral canal exposed; veins are semidiagrammatically shown at all levels from that of fatty pannicle inward to that of vena cava; the latter vessel remains only in renal and hepatic areas.

OBSERVATIONS AND DISCUSSION

Suprarenal arteries. Textbooks of gross anatomy and of surgical anatomy still lead us to believe that only three arteries supply a suprarenal gland, one minute vessel apiece from phrenic, aortic and renal sources. Actually, although the vessels do come from the sources just named, they are exceedingly numerous (Figs. 1 and 2). Dividing as they course toward the suprarenal, their number sometimes attains a total of 50 or more at the periphery of the gland. In some instances their origin is chiefly phrenic[2]; in others it is renal, the twigs being derived from the main renal artery, or, from a hilar division of the renal (Fig. 2, at arrow), with striking arborization at the margin of the gland. In some instances twigs from an accessory phrenic branch of the aorta add complexity to the pattern (Fig. 2). Ofttimes rami of suprarenal level cross to the upper pole of the kidney (Fig. 2), thus helping to render highly vascular the quadrilateral area above the true pedicle of the kidney.

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This brief report is published as read. A more detailed article, fully documented, is in preparation. The lengthier paper will present a full discussion of postnephrectomy death, of the hematogenous character of osseous and renal tuberculosis, and the possibility of retrograde venous flow, etc.

[1] Figure 8 in: Anson, B. J., Pick, J. W., and Cauldwell, E. W., *J. Urol.*, 1942, 47: 112–132.

[2] Figure 1 in: Pick, J. W. and Anson, B. J. *Anat. Rec.*, 1940, 78: 413–427.

Suprarenal and renal areas, therefore, cannot be divorced; nor can the genital visceral supply be regarded as independent of either of these, since a spermatic (or ovarian) artery may arise from a supernumerary renal. Even when the gonadal vessel arises from the aorta at the accustomed level, it may still be an element of the pedicle, in coursing transversely to pass through a hiatus in the renal vein (Fig. 2).

Suprarenal veins. While it is common to find suprarenal arteries multiple to an astonishing degree, it is likewise regular to find veins disposed in simplest possible arrangement, i.e., one vein for each suprarenal gland.

The suprarenal vein of the right side is exceedingly short (Fig. 3); it courses transversely to end quickly in the inferior vena cava. The vein of the left gland is longer (Fig. 4); it descends to the left renal, almost always receiving the inferior phrenic vein, and, often, capsular tributaries. It reaches the renal opposite the termination of the internal spermatic vein.

Thus it is clear that suprarenal arteries are numerous, the vein single, for each gland. There is, then, no similarity in pattern between suprarenal arteries and the associated veins. Nowhere in the human body are vessels of the two categories of blood vessel as discrepant in schema as they are in the supply to this endocrine gland.

Renal arteries. Supernumerary arteries to the kidney are of common occurrence; they are more likely to be present than absent.

The arrangement of renal arteries varies between wide limits. Commonly, the main renal artery is accompanied by lesser, accessory, renals (Fig. 1) which may give off an internal spermatic artery.

When the accessory renals arise from phrenic, main renal, or suprarenal artery, or in common with the spermatic, they go to the upper pole of the kidney, and they are small. When, on the contrary, they are large, the arteries are likely to be arranged in serial manner (Fig. 5), and to affect both poles as well as hilus of the kidney. They pass to the kidney in either precaval or postcaval course; some may be polar in termination. They may clasp the renal vein, or be removed therefrom by a considerable distance, in arising at the levels of the superior and inferior mesenteric arteries.[1]

It is clear, then, that the so-called renal "pedicle" may be a ladder of vessels which arise from the aorta over an area equivalent to the kidney's height.

Renal veins. The architectural pattern of the renal veins differs strikingly from that of the renal arteries.

Usually there is a single vein on the right side. However, there may be doubling (Fig. 3), or, in rare instances, even trebling (Fig. 10). In exceptional instances the right renal receives a single tributary, the internal spermatic. On the left side duplication of the renal vein is excessively rare. However, division of the single vein, en route to the vena cava is quite common (Figs. 5 and 9). In such course the divisions surround the aorta to form a circumaortic venous ring (Fig. 9). As the single renal vein leaves the left kidney, it splits to send one limb across to the vena cava in front of the aorta, the other obliquely downward behind the aorta to the vena cava. Seen from the front, the space outlined is not annular or oval, but triangular. The posterior limb itself may be bifid (Fig. 5), it may split locally to form a hiatus for transmission of a renal artery, or may communicate with the anterior limb by one or more of a set of small oblique channels (Fig. 6). The posterior limb, being retroaortic and, therefore, immediately prevertebral, is in a position to receive deep tributaries, of lumbar order chiefly (Figs. 5, 6, 9, and 11, at arrows).

Thus, it is evident that the veins do not match the renal arteries in number or in course; and while complexity in renal arterial pattern is expressed in multiplication of vessels, complexity in venous arrangement is the result of Y-shaped bifurcation of the renal vein, or of communication with neighboring veins, or of these circumstances combined. Intricacy of this nature is characteristic of the left side, and is dependent upon the greater length of the left renal vein and its intimate relationship to the psoas muscle, to the crus of the diaphragm, as well as to the vertebral column.

[1]Figures 1–6 in: Pick, J. W. and Anson, B. J. *J. Urol.*, 1940, 44: 411–434.

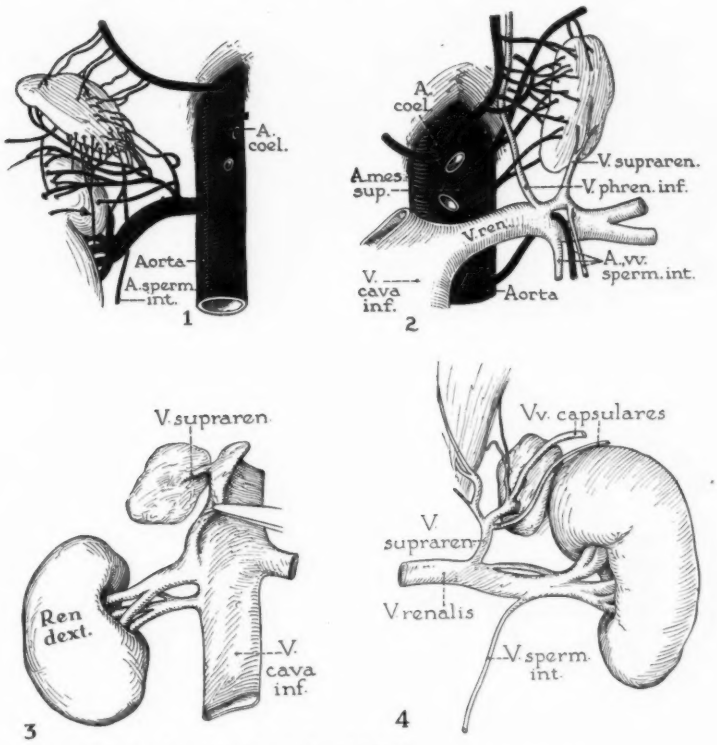
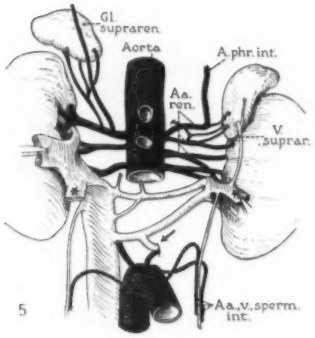


Fig. 1. Renal and suprarenal arteries; right side.
Fig. 2. Renal, suprarenal, and associated arteries and veins; left side.
Fig. 3. Renal and suprarenal veins; right side. Suprarenal vein, as regularly, is short; renal vein, paired, represents a relatively uncommon arrangement.
Fig. 4. Renal, suprarenal and tributary veins; left side. Renal vein, of "standard" type, receives suprarenal, phrenic and capsular drainage cranially; caudally it receives gonadal (here, spermatic) vein.

Even when the left renal vein, in addition to receiving visceral tributaries from the suprarenal gland and testis (or ovary), it is in a position to take dorsally placed somatic veins of the lumbar series. Such veins end in the renal so regularly that the standard "textbook" picture of left lumbar drainage into the vena cava actually represents a very uncommon venous scheme (Fig. 8). Much more frequently the second lumbar vein ends in the renal, not in the vena cava, sometimes through the spermatic as an intermediary (Fig. 7). Renal venous connections are often thoracic as well as abdominal, renal receiving a lumbohemiazygos vein. Thus intercostal blood is brought directly into the renal vein (Fig. 13).

Drainage into the renal is not limited laterally by the psoas muscle, since capsular veins from the perirenal tissue regularly empty into the renal, or into one or more of its immediate tributaries. Placed circumferentially in relation to the kidney they approach the renal pedicle from above and from below (Fig. 11). The capsular veins are prone to terminate in the nearest venous channels of axial course. Such vessels are the spermatic (caudally) and suprarenal (cranially); through these visceral veins blood from the special perinephric tissue and from the general retroperitoneal connective tissue of the left side of the abdominal wall is received by the renal (Fig. 11). Either of the two capsular veins may divide en route



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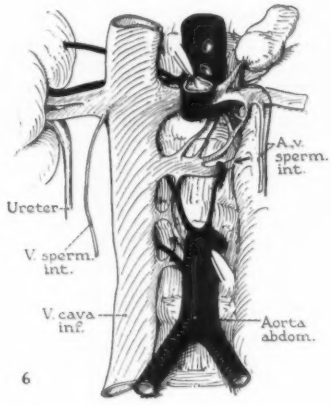

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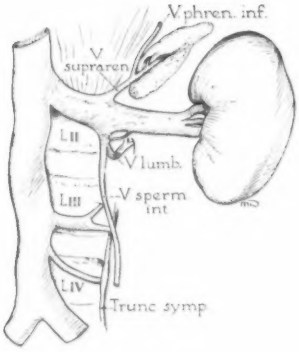

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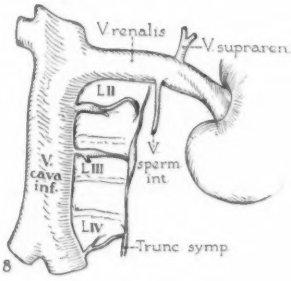

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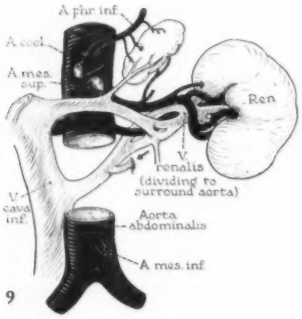

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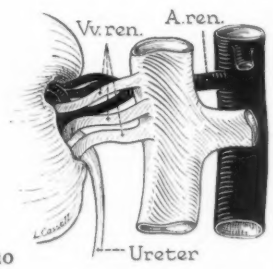

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Fig. 5. Renal arteries and veins, suprarenal arteries; right and left sides. Renal arteries are multiple on both sides; renal vein is single on right side, while on left a circumaortic venous ring is formed. Preaortic single vein has been cut, the ends (at asterisks) retracted; postaortic segment is split as it crosses vertebral column. Preaortic segment receives left spermatic vein, while caudal division of postaortic segment receives a lumbar vein (at arrow).

Fig. 6. Renal veins with tributary and otherwise associated vessels; both sides. Right renal vein single, but bifid, receives an internal spermatic at former's caval end. Left renals form an unusual type of circumaortic ring, the segments being connected through a small channel which receives a relatively large lumbar vein (at arrow) and lesser tributaries from prevertebral retroperitoneal tissue, etc. Internal spermatic artery, as a constituent of left renal vascular pedicle, hooks round suprarenal tributary of left renal vein.

Fig. 7. Renal vein and tributaries; left side. Left renal vein receives, cranially, suprarenal vein, and through latter, inferior phrenic vein; caudally it receives a common channel for second lumbar vein and internal spermatic vein (third and fourth lumbars are directly caval in termination).

Fig. 8. Renal vein and regular tributaries; left side. "Textbook" pattern (as in specimen in Fig. 4), in contrast to commonly encountered type with lumbar drainage (see Figs. 5 to 7).

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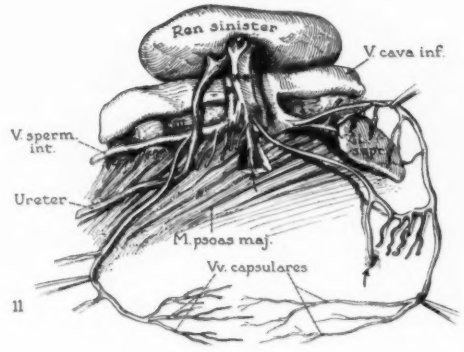

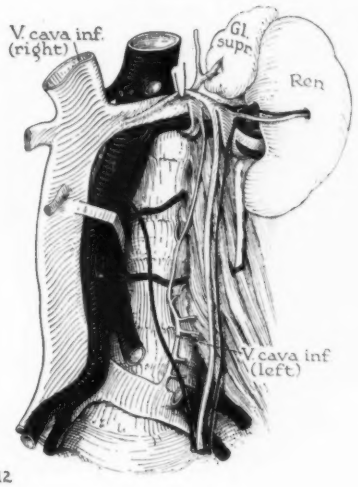

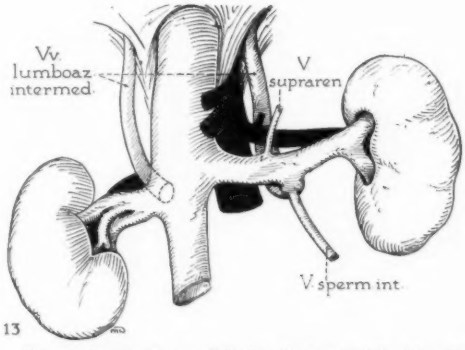

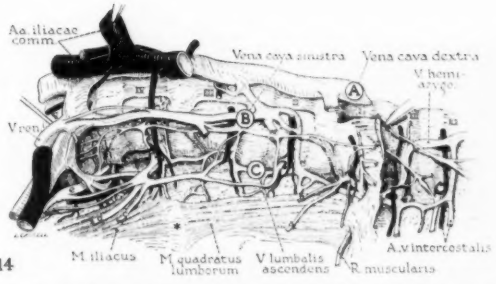

Fig. 9. Renal veins and their tributaries; left side. Circumaortic venous ring made up of segments of equal size (in contrast, Fig. 6); each segment locally split; lower segment receives second lumbar vein (at arrow).

Fig. 10. Renal veins; right side. Rare arrangement in which renal veins occur in triplicate.

Fig. 11. Renal and associated veins; left side. Circumaortic venous ring with widespread drainage, chiefly through capsular tributaries (*, preaortic arm of "ring," **, postaortic arm; aorta removed). Superior one of capsular veins divide to send divisions into renal indirectly through suprarenal vein and through second lumbar vein (at upper arrow); inferiorly placed capsular vein also enters indirectly, by becoming confluent with internal spermatic vein. Caudal division of superior capsular and intercostal drainage (at lower arrow), thoracic vessels piercing attached margin of diaphragm.

Fig. 12. Renal and tributary veins; left side. Left renal vein receives on its caudal aspect small left inferior vena cava. Persistent left vena cava extends from left common iliac vein to left renal vein, receiving, in ascent, small veins from axial musculature and second lumbar vein (cf. Fig. 14).

Fig. 13. Renal veins; both sides. Large veins from thorax (intermediate lumboazygos veins) descend to renal level. Vein of right side empties into renal where latter joins inferior vena cava; vein of opposite side enters left renal vein after passing dorsal to corresponding artery and after receiving internal spermatic vein.

Fig. 14. Caval and ascending lumbar venous channels; left side. Venae cavae (normal at *A*, anomalous left at *B*) are brought into communication by retroaortic limits of circumaortic venous ring which is also connected with azygos system of veins by channel passing behind diaphragmatic arch; third vertical vessel, ascending lumbar vein (at *C*) communicates, through transverse channels, with anomalous vena cava and with venous "ring."

to the renal pedicle, and may communicate with intercostals.

Now it should be pointed out that the lumbar veins drain more than the psoas major and adjacent muscles. Typically, each receives an intervertebral vein from the spinal cord, meninges, vertebrae, and vertebral ligaments. These transversely coursing lumbar veins interconnect at right angles to form a longitudinal vessel, which is the ascending lumbar vein, lodged in the sulcus between the psoas major muscle and the transverse processes of

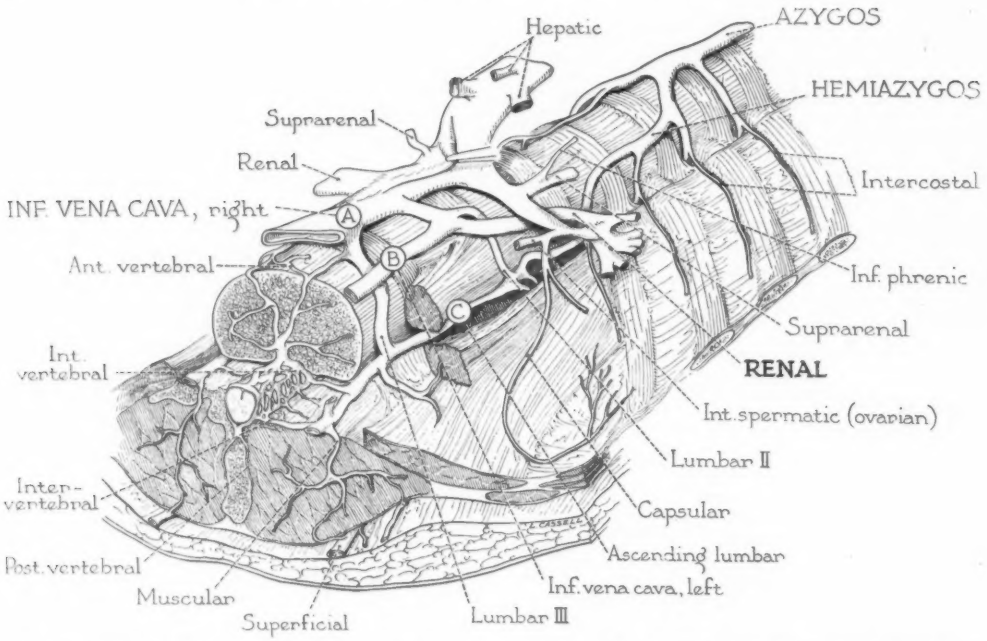

Fig. 15. Veins of dorsum of trunk at renal level; recording complexity of venous pattern on left side as compared with simplicity of drainage schema on right. Semidiagrammatic composite of three specimens (including those shown in Figs. 11 and 14). On right, suprarenal and renal veins empty directly into inferior vena cava (at *A*, in approximately median position upon vertebral column). On left, communicating directly or indirectly with preaortic or postaortic limb of circumaortic venous ring are the following: left inferior vena cava (*B*, lodged in sulcus between vertebrae and psoas muscle); ascending lumbar vein (*C*, coursing with substance of psoas); hemiazygos vein and its intercostal tributaries; inferior phrenic and suprarenal veins; capsular veins, with lesser tributaries coursing in retroperitoneal layer; lumbar veins, with tributaries from external and internal vertebral plexuses, from the dorsal axial musculature and from the superficial fascia and integment of the back.

the vertebrae. Superiorly the ascending lumbar is continuous with the azygos and hemiazygos trunks of the thorax (Fig. 14). The ascending lumbar is uncritically regarded as an uninterrupted vertical channel. Actually, it is frequently defective in its middle portion, so that a lower part descends to empty into the left common iliac vein, an upper part into the renal and hemiazygos. In full form it would outline, along each vertebral segment, a posterior side of a quadrilateral figure, whose medial boundary would be the inferior vena cava and whose superior and inferior boundaries would be adjacent lumbar veins.

The most complex schema is produced when a circumaortic venous ring occurs in association with an anomalous left inferior vena cava (Fig. 14; cf. Fig. 12). Two caval channels (Fig. 14, at *A* and *B*) then exist side-by-side, brought into communication by the retroaortic limb of a venous ring and left common iliac vein. The third of these vertical channels is the ascending lumbar vein (Fig. 14, at *C*). When present, a left inferior vena cava is likely to be small (Fig. 15). Rarely (2 cases in the authors' 400 specimens) the venae cavae are of equal size; still rarer are cases (1 in 400) in which the left cava is oversize, while the right is small. In each of the three types, pelvic blood is carried into the left renal vein from the left common iliac.

Wherever there is renal tissue there will be arteries from an adjacent portion of the aorta or its large iliac divisions, and veins returning to vena cava or iliac vein at near level—no matter how aberrant may be the form of the ped-

icle as a result of peculiarity in form or position of the kidney. Two examples will suffice to illustrate this point. In fused, or horse-shoe kidney, the vessels follow the semilunar margin of the organ—not only as multiple arteries and veins to the elongated renal sinuses of the two sides, but as a spray of arteries to the isthmus, which assume, totally, the form of a half wheel. In ectopic kidney of pelvic type[1] the organ lies against the branches of the common iliac artery; low aortic renal arteries descend to the kidney and veins and pass to the common iliac or to the caudal portion of the inferior vena cava.

CONCLUSIONS

From the above observations certain conclusions of an anatomical nature were reached, and some opinions of practical nature may be ventured.

Suprarenal arteries are very numerous, although individually small; they converge upon the suprarenal gland, placing the gland in the position of a visceral hub of a multispoked vascular wheel. The venous plan is simple, there being, with exceedingly rare exceptions, a single vein for each gland.

Supernumerary renal arteries of large size are common as are also lesser arterial branches in the suprarenal area. Accessory renal veins are infrequent. Complexity in the venous pattern is expressed not in duplication of vessels, but in continuity of the renals with veins draining any or all of the surrounding structures.

When the usual communications of the left renal vein are grouped, as if the observer were viewing a composite of several selected specimens, the true expanse of the renal field of vascular influence becomes apparent (Fig. 15). The left renal vein is then found to be situated at the core of an impressive set of veins and venous plexuses: inferior phrenic and suprarenal tributaries enter from above; from below and to the side come spermatic (or ovarian), capsular, lumbar, and ascending lumbar veins and the anomalous vena cava. Additionally, communication is made with azygos and hemiazygos veins (usually through lumbars) and with the extensive set of internal and external vertebral plexuses by way of the intervertebrals and the lumbars.

These widespread connections bring the following structures into venous relationship with the kidney: the respiratory diaphragm; suprarenal gland, testis, ductus deferens and ureter; the capsular and the general retroperitoneal tissue; the peritoneum; lumbodorsal axial and appendicular muscles (psoas, major, sacrospinalis, quadratus lumborum, latissimus dorsi and trapezius); the superficial fascia and skin; the ribs, intercostal muscles, thoracic subserous tissue; pleura and pericardium; the vertebrae, their discs and ligaments; the spinal cord and its meningeal coats; the viscera, musculature and skeletal elements of the pelvis; the lower extremities.

Not only, then, is there regularly present greater than the expected number of renal arteries, to render nephrectomy basically hazardous, but also veins in such profusion as to carry infectious material and neoplasms widely, and to convey to the kidney organisms of disease from distant body areas.

On the basis of the anatomical observations above recorded, clinical conditions of the order just mentioned may be explained. Three examples will suffice to suggest probabilities.

For example, it is known that postnephrectomy death in renal tuberculosis is sometimes caused by a meningitis. Spread of the bacilli would be possible by way of the following succession of veins (Fig. 15): renal, lumbar and intervertebral veins, internal vertebral plexuses through thoracic and cervical regions, cranial dural sinuses and meningeal veins.

Similarly, in Pott's disease, the hematogenous migration may occur through the following venous channels: renal veins, lumbar and intervertebral veins, posterior and anterior vertebral plexuses, and, terminally, the veins within the spongious bone of the vertebrae.

In the spread of neoplasms of the medullary portion of the suprarenal glands, tumors of the right gland tend to metastasize to the liver, while tumors of the left frequently metastasize to the skull, and occasionally to the sternum and ribs. Spread may be effected by way of venous and lymphatic pathways, as well as by

[1]Figure 1 in: Anson, B. J., Pick, J. W. and Cauldwell, E. W. *J. Urol.*, 1942, 47: no. 2, 112–132. Also, figures in, Anson, B. J. and Riba, L. W. *Surg. Gyn. Obst.*, 1939, 68: 37–44.

contiguity. The left suprarenal vein ends not in the vena cava, but in the renal; the latter communicates with azygos and, thereby, with intercostal veins, and the internal mammary. The left renal vein is also continuous with lumbar veins and the vertebral plexuses; the latter connect with the dural and, finally, the diploic veins in the flat bones of the skull. Through spread of cancer cells by way of the veins of the thoracic and of the cranial systems, the characteristically spotty involvement of ribs, sternum, and bones of the skull may be explained.

These examples will serve to remind the reader that there is still much to be learned about the renal area. The anatomist's study is soundest when he limits his assignment to the task of charting channels; since his dissections need not be done in haste, the anatomist finds it possible to demonstrate vessels which are not easily traced in the progress of post mortem examination or surgical operation. His results, interpreted with the co-operation of pathologist, internist, and urologist, should be of service in both medicine and surgery.

SIMPLIFIED REPAIR OF THE COMMON DUCT

Use of Umbrella Catheter to Produce Internal Biliary Fistula

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IN surgical repair of the common duct internal biliary fistula may be successfully produced by use of an umbrella catheter. If a dilated vestige of the common duct remains into which the head of an umbrella catheter may be inserted, the entire duct may be reconstructed. The operative procedure is safe, requires less technical skill than other methods, and achieves better results, with fewer complications.

In successful repair of the common duct over a rubber tube, it is necessary to secure both ends of the tube in such a manner that it will remain in place permanently without the aid of sutures. When properly placed, the catheter will not be extruded. We are quite certain from our own investigations that these rubber tubes will last for many years. Biliary obstruction is the only reason for removal. We have found that the new vitallium tubes are too short, must be held in place with sutures, and do not have enough flexibility. In 1945, Bettman and Tannenbaum reported a case in which an incrusted vitallium tube obstructed the common duct and had to be removed.

A new, natural rubber, umbrella catheter should be used for the reconstruction. The umbrella is inserted through a small stab wound in the bulging proximal end of the common duct to prevent the tube from slipping into the duodenum (Fig. 6). The catheter is then manipulated, transduodenally, through the opening at the distal end of the common duct, if the opening can be found (Fig. 1). If not, the catheter is inserted through a minute stab wound into the duodenum. This stab wound is made small enough to grip the catheter, which could obviate the necessity of the customary silk pursestring suture. The catheter extends far enough into the lumen of the duodenum to prevent extrusion that might otherwise occur in postoperative traction due to position of the patient or visceral movements. The duodenum need not be drawn close to the liver, as considerable space may be bridged by the tube. All available viscera and fat are used to cover the catheter. Sulfathiazole powder (75 to 150 grains) is sprinkled along the course of repair. Closure is routine, with one Penrose drain brought through the abdominal wall.

There is little or no bile drainage, and no duodenal fistula occurs in cases repaired in this manner for three reasons: (1) the catheter is fitted securely at both ends and held in place with a silk pursestring suture, (2) there will be no intraductal pressure; the valvular action of the ampulla of Vater is eliminated when the catheter is inserted into the duodenum, and (3) sulfonamide compounds aid in combatting infection.

In 1 patient the umbrella catheter has been in place for 3 years (Fig. 7). Whether it is incrusted or not, we do not know. This patient has no symptoms of obstructive jaundice and is normal except for an occasional mild attack of indigestion which may *not* be due to regurgitation of duodenal contents into the biliary tract. If these mild attacks are due to cholangitis, they are not as serious as attacks of obstructive jaundice or by the recurrence of strictures. The latter two conditions frequently arise in the usual methods of common duct repair and necessitate repeated surgical procedures. The relatively minimal effect of cholangitis has been proved by patients who apparently have been well for many years following cholecystoduodenostomy.

The common duct could not be located in a second case. Only the stubs of the right and left hepatic ducts remained. At operation a stiff T tube was inserted into the hepatic ducts; the catheter portion was introduced into the duodenum, as described previously (Fig. 2). This tube slipped free from the ducts into the intestinal tract some time between the eighth and twelfth postoperative weeks. Roentgenologic examination, in the eighth week showed the tube in place but, on similar

Fig. 1. An umbrella catheter bridges a defect in the common duct.

Fig. 2. A T tube sidetracks the bile from the hepatic ducts into the duodenum.

examination, in the twelfth postoperative week it was absent. As this patient's condition was good and has remained good, with no symptoms of obstructive jaundice present, it would seem that the internal biliary fistula is functioning properly. This was true, when the patient was last checked 14 months after operation. This particular case shows how quickly internal biliary fistulas will form and function. It is apparently true that some internal biliary fistulas (if the tube is not removed or extruded too early) *do* function well and are not obstructed by cicatricial contraction. The percentage of internal biliary fistulas that will close by cicatrization is not known. It is likely that the pressure from the flow of bile aids in keeping many fistulas patent.

Many methods of common duct repair have been described. Sullivan, in 1909, bridged

Fig. 3. X-ray film of Case 7 shows umbrella catheter in place 3 months after surgery.

Fig. 4. Shows the cholangiographic study of Case 10 with complete stenosis of the common duct.

gaps in the common duct with a rubber tube. The omentum was wrapped and sutured about the tube. He concluded that the straight rubber tube should not pass into the lumen of the duodenum if required to stay in place for a long while. In later observations he concluded that this type of operation should be suitable for some cases of carcinoma extending up the duct, the drawback being that the opening was not valvular. The Mayo technique of direct anastomosis, with a semilunar opening into the duodenum, was popular because of the valvular effect obtained by the semilunar duodenal opening. Walton found the duct was often so short that the direct implantation into the duodenum was difficult. Lahey has reported best results from repair around a T tube. He also used a straight tube for repair and removed it after 7 years of normal biliary function and replaced it with another which is still functioning satisfactorily. Fascial repair is described by Davis and Lewis and others.

Fig. 5. Shows the umbrella catheter in place in Case 10.

We have had 10 cases in which umbrella catheters have been used to repair the common duct. In 7 cases the tube was used to bridge malignant lesions extending from the junction of the cystic duct downward to and including the ampulla of Vater and the pancreas. Anastomosis between the common duct and the duodenum was made quickly with an umbrella catheter. Jaundice and intense itching disappeared and the bile was retained in the intestinal tract. Six of these patients have

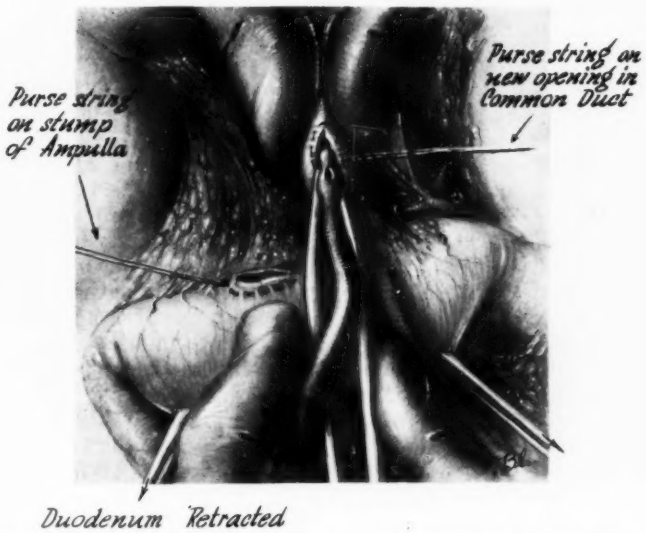

Fig. 6. Shows method of inserting head of umbrella catheter into side of duct.

Fig. 7. Roentgenogram of Case 8 taken 3 years after operation.

died from metastatic carcinoma but were relieved of symptoms of obstructive jaundice.

The seventh patient is still alive. She had cholelithiasis and early adenocarcinoma at the junction of the cystic and common duct. On May 5, 1945, we removed her gall bladder and inserted a T tube in the common duct above the tumor. Her general condition at the time was not good and icteric index was 54. On January 14, 1946 she pulled out the T tube and immediately developed symptoms of biliary obstruction with an icteric index of 60 and intense itching. A second operation was performed on January 24, 1946. At this time we removed the common duct from the junction of the hepatics well down to the ampulla. The distal end was doubly ligated. The common duct stub was connected to the duodenum with an umbrella catheter. Biopsy of an enlarged regional lymph node showed no malignant condition. The liver showed no gross evidence of metastasis. On April 24, 1946, twelve weeks following operation, this patient's icteric index was 7. Her weight and general condition were normal. It was evident, on roentgenologic examination on April 30, 1946 that the umbrella catheter was in the same place as it was at the time of operation (Fig. 3).

In Cases 8, 9, and 10 there was no evidence of malignancy, the obstruction was due to benign causes, and the patients are enjoying a normal existence after similar operations have been carried out.

In Case 10 the patient was first operated upon elsewhere on November 1, 1942. The gall bladder containing stones was removed. Following the operation there was bile drainage until December 1, 1942, when it ceased and was immediately followed by symptoms of obstructive jaundice. In January, 1943 in a second hospital, a surgical attempt to relieve the obstructive jaundice failed. In June, 1943 in the same hospital, a second attempt to relieve the obstructive jaundice failed. In March, 1945 (3 years and 5 months following the first operation) in a third hospital a metallic tube was inserted in the common duct. There was a marked improvement in jaundice and general condition for 60 days. In June, 1945 the patient again became jaundiced and x-ray examination showed absence of the metallic tube.

In May, 1946, 4 years and 7 months following the first operation, the patient entered the hospital. There were marked signs of obstructive jaundice and pain that required morphine, ¼ grain every 3 hours. May 13, 1946 after the usual preparation of a severely jaundiced patient with proved marked liver damage, an umbrella catheter (Fig. 5), was inserted between the bulged proximal end of the common duct and the duodenum. Before closing the wound, cholangiographic examination (Fig. 4) shows the hepatic radicles open and the common duct completely obstructed. This patient was dismissed from the hospital on the eighteenth postoperative day. The icteric index was normal and, with the aid of a psychiatrist, no morphine had been given for 2 days. We are quite confident that the use of the umbrella catheter in this case will restore this individual to as nearly a normal existence as is possible after 4½ years of nearly complete obstructive jaundice.

We wonder how the complications following this type of repair will compare with those

following other types of procedure, such as: (1) transplantation of an internal biliary fistula, (2) end-to-end anastomosis of the common duct, (3) hepaticoduodenostomy, (4) choledochoduodenostomy, and (5) repair of the duct over a T tube.

SUMMARY

A simplified procedure has been presented for repair of the common duct by means of an umbrella catheter to form an internal biliary fistula.

1. An umbrella catheter is placed between the proximal and distal stubs of the common duct. The catheter is not removed unless obstruction occurs.

2. Incrustation of the tube is probably diminished by the direct and unobstructed flow of bile into the intestine, due to the absence of the ampulla of Vater.

3. In the 10 cases in which this operation was performed, no umbrella catheters have been displaced, there has been no bile drainage, and no duodenal fistulas have developed.

4. In 1 case (Fig. 2) the internal biliary fistula is functioning 2 years after loss of the tube in the intestine.

5. We believe that cicatricial contraction is less likely to occur the longer the tube remains *in situ* before it is removed.

6. Cholangitis is not a complicating factor in these cases.

7. It is not known what percentage of internal biliary fistulas will close or how long they will stay open.

The method which we have described might be called nonsurgical according to well known operative procedures, but our experience continues to be encouraging. We believe this to be a most satisfactory method of repair of the common duct.

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UNILATERAL EXOPHTHALMOS, AN EARLY SIGN IN THYROTOXICOSIS

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UNILATERAL exophthalmos appearing as an early sign of hyperthyroidism is not rare. It is very likely that the first physician to whom such a patient applies for help will be an ophthalmologist and several of the patients in our series were first seen by ophthalmologists who suspected the presence of thyrotoxicosis. Other such patients however, apply to their family doctor for diagnosis. Exophthalmos, either unilateral or bilateral, occurring as the first sign of hyperthyroidism and preceding other clinical and laboratory manifestations of hyperthyroidism, occurs often enough for any examining doctor to keep this possibility in mind. Unilateral exophthalmos may be the only sign of incipient toxic diffuse goiter and may precede by months all other subjective and objective findings.

Unilateral exophthalmos may be caused by many conditions but unless the cause is otherwise obvious hyperthyroidism should always be considered. Dixon believes that thyrotoxicosis is a relatively common cause of mild unilateral exophthalmos which he says is almost always retraction only of the upper lid and no other abnormality. Other causes of unilateral exophthalmos as pointed out by Davis and Martin are: intraorbital inflammatory disease either primary or secondary to an infected paranasal sinus, paralysis of the extraocular muscles, cavernous sinus thrombosis, congenital anatomic defects, angiomas or aneurysm either within or behind the orbit. Of these vascular lesions and tumors are the most frequent causes of unilateral exophthalmos.

Cavity mentions that the term exophthalmos is often used loosely and sometimes is confused with a retraction of the upper lid simulating a protruded eyeball (Dalrymple's sign). He believes that many cases of unilateral exophthalmos are simply incomplete in terms of bilateral involvement. Not only is this true, but also many cases of bilateral exophthalmos show some difference of proptosis in the two eyes. Most cases of unilateral proptosis in thyrotoxicosis will, provided the disease process is not checked, eventually show similar changes of the other eyeball. Ruedemann explains the apparent unilaterality of exophthalmos under these circumstances as follows. He thinks the eyes are usually in a normal anterior posterior position with retraction of the lid on one side and with a partially successful attempt of the orbicularis palpebra to overcome the levator spasm of the other side. In his series of cases of real exophthalmos in hyperthyroidism the condition was always bilateral.

Cavity reported 3 cases in which unilateral exophthalmos was the first sign in Graves' disease and the diagnosis was not established until after intervals of 6, 8, and 20 months respectively. Ellett reported 2 cases with unilateral exophthalmos as the presenting sign and symptom in Graves' disease. His second case had a normal basal metabolism and exploratory operation was performed with removal of tissue from the muscle cone of the orbit. This was reported to be an epithelial like medullary tumor infiltrating the orbital fat. An orbital decompression was done according to Ellett and only hypertrophied extraocular muscles found. Two years later this patient had symptoms of hyperthyroidism and the basal metabolic rate was plus 46. This case and 1 in our series emphasize the fact that unilateral exophthalmos may appear as an early sign in thyrotoxicosis when no other signs or symptoms are present. The possibility of misdirected surgery on the eye under such circumstances is obvious.

The cause of exophthalmos in Graves' disease is still obscure. Within recent years many

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investigators including Shockaert, Loeb and Friedman, Pochin, Paulson, Arid, and others have demonstrated that thyrotropic hormone from the anterior pituitary gland when injected into guinea pigs will produce exophthalmos. Dobyns has shown that thyroidectomy alone will cause increased prominence of the eyes in guinea pigs. Pochin in his studies found no difference in the prominence of the eyes between the thyroidectomized and the nonthyroidectomized guinea pigs following injections of the thyrotropic hormone. Dobyns studied the exophthalmos producing effect of several different preparations of thyrotropic hormone and in addition the effect of the presence or absence of the testes and the thyroid on the development of exophthalmos. He found that antuitrin T caused exophthalmos in guinea pigs. A crude thyrotropic product produced both thyroid hyperplasia and exophthalmos, whereas a purified product produced only thyroid hyperplasia. Dobyns also found that orchidectomy had no inhibitory effect on the exophthalmos produced by the thyrotropic hormone.

Naffziger has shown that exophthalmos after thyroidectomy may become progressive, a fact noted by many observers. He reported such a case with the pathological findings. The exophthalmos was due to great volume increase in the extraocular muscles. This increase was not a true muscle hypertrophy but a result of fibrosis following edema. Rundle and Pochin in a study of the orbital tissues in thyrotoxicosis conclude that exophthalmos in Graves' disease is accounted for quantitatively by an increase in bulk of the retrobulbar tissues. The increase was relatively greater in the eye muscles of which the average fat content was doubled in a series of 17 thyrotoxic cases. The changes are most marked in the levator palpebrae superioris muscle which is known to be responsible for lid retraction. Increase of fat in the orbital fibro-fatty tissues is, however, responsible for most of the increase in bulk. Arid defines malignant exophthalmos as the progressive and alarming proptosis which occurs in a small group of patients usually after thyroidectomy and in the presence of a low basal metabolic rate. In these cases he found the extraocular muscles to be enlarged from three to eight times their normal size. Grossly the musculature of the orbital muscle cone is observed to be finer, pale, and edematous. Various stages of degeneration were observed histologically with interstitial edema, and proliferation of small round cells which showed a tendency to accumulate around blood vessels. Fibrosis appeared more dense and extensive in the advanced cases. Arid produced exophthalmos in guinea pigs by injection of the thyrotropic hormone and found the exophthalmos due to myopathy of the extraocular muscles. Smelser (20) produced experimental exophthalmos in thyroidectomized guinea pigs by injection of extracts of the anterior pituitary gland. His study revealed a hypertrophy of the orbital fat almost entirely due to an increase in the water content of this tissue. No change in the lipid content of the orbital fat was noted. There was also a marked increase in the water component of the muscles. Smelser (19) after further studies states that it is not clear whether changes in the orbit are primary causing exophthalmos or secondary resulting from it. He concludes that the hypertrophy of the extraocular muscles in guinea pigs with experimental exophthalmos produced by injection of anterior pituitary extract appears to be a sequence of the exophthalmos, however, there is some indication that the extraocular muscles are affected directly in the same manner as the fat. Smelser (19) points out that changes in the extrinsic eye muscles have been emphasized in the literature since the observations of Burch and Naffziger who noted hypertrophy of the muscles, marked edema, perivascular infiltration with round cells and many atrophic muscle fibers suggesting Zenker's degeneration.

Mulvany states that some cases of hyperthyroidism go for long periods of time without a definite diagnosis. He cites 2 cases of patients under his care for 6 and 10 years respectively with basal metabolic rates ranging from plus 15 to plus 40, he says, without ill effects. In these cases Mulvany warns that removal of the thyroid may accentuate the exophthalmos by stimulating the pituitary gland.

It is our experience that immediately following thyroidectomy in such cases exophthalmos

Fig. 1.

Fig. 2.

Fig. 1. Man aged 51 years with unilateral exophthalmos. For 4 months this was the only subjective or objective sign of toxic diffuse goiter, which later manifested itself characteristically (Case 2).

Fig. 2. Patient with severe exophthalmos which began 1 year ago in her remaining eye (Case 1). She has moderately severe systemic signs of hyperthyroidism. The right eye was removed 15 years ago under a diagnosis of retrobulbar sarcoma—the accuracy of which diagnosis now becomes doubtful. The impression is that the exophthalmos of the right eye was an initial sign of a long latent hyperthyroidism.

may be more marked but as weeks and months pass the prominence of the eyes diminish and the eye returns to normal anteroposterior position much more surely than if the case is neglected and thyroidectomy deferred. Indeed, extreme exophthalmos after adequate thyroidectomy for toxic diffuse goiter rarely fails to improve no matter how severe it may be. The gradual subsidence may take months or as long as 2 years.

Numerous laboratory investigators in the past working with guinea pigs have demonstrated exophthalmos by sympathetic nerve stimulation. To date there has been no proof that this is a factor in the production of exophthalmos in humans, although there are some who feel that the sympathetic nervous system plays a part in this condition. As evidence against the sympathetics playing a part in the production of exophthalmos Brain reported a case history of a patient suffering from paralysis of the ocular sympathetic outflow as a result of syringomyelia who later developed Graves' disease and showed both exophthalmos and retraction of the upper lids.

The following 5 cases of unilateral exophthalmos with thyrotoxicosis were observed on our private services.

CASE 1. A 47 year old white female first noticed prominence of her left eye in January 1921. If any other symptoms of hyperthyroidism were present at that time they were apparently overlooked. In October 1931 her left eye was removed and the pathologic report was small round cell sarcoma. The authors have been unable to locate the original pathologic sections. Following the operation the patient was given radium treatments. Fourteen years later she was first seen by us. At that time she noticed her right eye becoming prominent and she began to complain of nervousness. Examination by the ophthalmologist failed to disclose any cause for the exophthalmos. The basal metabolic rate was plus 34. The patient's symptoms were mild but consistent with the diagnosis of hyperthyroidism. She did not report back until April 1946, at which time she had a basal metabolic rate of plus 31. Thyroidectomy was advised but as yet has not been performed. It is probable that the small round cell infiltration in the orbit was the result of exophthalmos in this patient, apparently an initial sign of a toxic goiter which only became obvious years later with the then associated exophthalmos of the remaining eye.

CASE 2. A 51 year old white male was seen by an ophthalmologist in July 1942 because of a left unilateral exophthalmos of 7 months' duration. He was referred to us and at that time the patient had no symptoms of thyrotoxicosis and the basal metabolic rate was normal. Physical examination was negative except for a left unilateral exophthalmos. It was suspected that the unilateral exophthalmos was an early and only sign of incipient hyperthyroidism. This, however, could not be substantiated at that time. The patient was seen again in December 1942 and a slight exophthalmos of the other eye was noted and the prominence of the left eye was more pronounced. The patient exhibited a slight tremor of his extended

Fig. 3. These 3 photographs of a patient who had had a thyroidectomy in January, 1942, were made May, 1942, February, 1943, and March, 1944. The first photograph shows marked exophthalmos, chemosis of the conjunctiva, and edema of the lids. The second photograph shows that the exophthalmos and edema have subsided but ophthalmoplegia is the residual of long continued severe exophthalmos. The third photograph shows the result after a "tuck" operation performed by Dr. William B. Clark. The strabismus has been obviated and the motions of the eyes are perfectly synchronized. There are two lessons to be gained from these findings. First exophthalmos, even if severe, may subside after thyroidectomy even though a long period is required; second, a "tuck" operation for squint is sometimes of benefit in ophthalmoplegia due to long continued exophthalmos of hyperthyroidism.

fingers and the basal metabolic rate was elevated plus 18. Thyroidectomy was performed in January 1943. The pathological report was hyperplastic thyroid with areas of lymphoid infiltration. Following operation the exophthalmos progressed. He was not seen again until 1946. During this period of 3 years the exophthalmos had become severe and he went to a medical group in an adjacent state. There a Naffziger operation was done. The right orbit only was unroofed. Following this both eyes receded. However, osteomyelitis of the skull resulted with considerable loss of bone in the right frontotemporal region. His health is now good but he has a depression and bone defect in the right frontal area.

CASE 3. A white female aged 27 years was referred by an ophthalmologist to whom the patient had gone because of a left unilateral exophthalmos. This patient noticed a prominence of her left eye 4 months before reporting for examination. The prominence of her left eye had gradually increased and 2 months after she first noticed the condition of the eye she began to suffer from extreme nervousness and irritability with crying spells. The patient stated that she had been nervous all her life so the increase in nervousness did not alarm her as did the exophthalmos. She had lost no weight and had no other complaints. On physical examination the patient was so nervous she was constantly moving her limbs and body and interrupting the history taking by outbursts of almost hysterical laughter. There was a moderate degree of exophthalmos of the left eye and the thyroid gland was firm, smooth and slightly enlarged. There was a marked tremor of the extended fingers and the skin was warm and moist. The basal metabolic rate was plus 35. This patient was given 0.4 gram of thiouracil daily for 2 weeks and then admitted to the hospital. During the second week of thiouracil therapy 10 drops of Lugol's solution was given 3 times daily. After 1 week in the hospital on Lugol's solution thyroidectomy was performed. The pathological report was hyperplastic thyroid. She made an uneventful recovery and when recently seen, 4 months after the operation, was free of signs of hyperthyroidism, and the unilateral exophthalmos had subsided.

CASE 4. A negro female, aged 30 years, was seen because of a swelling in her neck of 1 month's duration. On examination the patient was found to have a right unilateral exophthalmos, the thyroid gland was enlarged, firm, and smooth. There was no tremor or other findings of thyrotoxicosis. The patient had not noticed the prominence of her eye but stated she had been nervous for the past 4 months and had lost 15 pounds in weight. She attributed this to worry over the death of her child 4 months previously. A friend of the patient had noticed the prominence of the right eye for several months but did not know the exact length of time. This patient was prepared with thiouracil and Lugol's solution and thyroidectomy was performed in March 1946. She made an uneventful recovery and was last seen 3 months after the operation when the condition of the eye had not changed. Later information on this patient has not been obtained.

CASE 5. A white woman, aged 59 years, was seen by an ophthalmologist because of unilateral exophthalmos. When first observed by us this patient had the classical signs and symptoms of thyrotoxicosis. She did not know how long her eye had been prominent but her chief concern was the unilateral exoph-

thalmos. Thyroidectomy was performed. One year later the patient was examined. The basal metabolic rate was minus 16, she had gained 15 pounds in weight and the exophthalmos was improved. The patient was again seen 4 years and 8 months after the operation and the exophthalmos showed further improvement.

COMMENT

Some phases of the problem of exophthalmos in exophthalmic goiter are not clearly understood; some are debatable. The cause of exophthalmos is not established but from experimental studies made by the authors cited and others, it would appear that a factor in the anterior pituitary secretion has the property of producing exophthalmos and the same or a different factor has the property of inducing hyperplasia of the thyroid gland. The latter was observed in experimental work on dogs performed by one of us (Howard Mahorner). Whatever the exciting factor for exophthalmos the pathogenesis is not at all clear. Is the first effect a weakness of extraocular muscles, a contraction of Mueller's muscle or an edema of periorbital tissues, or does one of these changes precede another only to be replaced later as the cause of sustained exophthalmos? Over activity of the orbicularis muscle of Mueller could be an early change; later edema of periorbital fat and edema and weakness of periorbital muscles could further enhance the process.

There is little doubt that in some cases of exophthalmic goiter, the immediate effect of thyroidectomy on the exophthalmos is to make it worse. Some observers (Mulvany and Means) believe that the cases in which such an untoward effect is to be expected may be identified before operation. The identity, Means says, is to be recognized in patients with exophthalmos and mild signs of hyperthyroidism and relatively low basal metabolic rates. Means goes so far as to advise that such cases be treated medically and that surgery is contraindicated. This does not agree with our concept of what can be expected in subsidence of exophthalmos after thyroidectomy. Perhaps the general but erroneous impression exists that following thyroidectomy for exophthalmic goiter the exophthalmos immediately subsides. On the contrary even in cases with high basal metabolic rates and exophthalmos, the exophthalmos is frequently a little worse in the weeks immediately after operation. Only after many weeks and months does the exophthalmos gradually subside and under these circumstances usually the eyes return to normal. After adequate thyroidectomy improvement of severe exophthalmos may be expected to continue to normal, even though the time required for this accomplishment is over a year and up to 2 years. It is our impression that thyroidectomy is indicated for toxic goiter when the diagnosis is made, even though the associated exophthalmos is accompanied by a basal metabolic rate which is not even moderately high.

Because of the long time over which improvement in exophthalmos after thyroidectomy may occur radical procedures such as the Naffziger operation should be deferred unless extreme proptosis greatly jeopardizes the sight of the eye.

Another interesting but little known fact concerning exophthalmos from exophthalmic goiter is that manifest strabismus resulting from ophthalmoplegia due to long sustained exophthalmos may be corrected after subsidence of orbital edema by a "tuck" operation. Figure 3 shows a beautiful surgical result obtained in such a case by Dr. William B. Clark.

SUMMARY

We have reported 5 cases of unilateral exophthalmos due to exophthalmic (toxic diffuse) goiter. In all of these cases the unilateral exophthalmos was a prominent—in some it was the only—feature of the disease noticed by the patient.

A discussion of the causes and some of the clinical features of exophthalmos due to toxic goiter is presented.

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THORACICOABDOMINAL APPROACH TO THE UPPER ABDOMEN

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THE organs of the left upper abdomen have always been difficult surgical problems because of lack of proper exposure. In working through an abdominal approach the surgeon is handicapped because the costal arch prevents adequate retraction. On the other hand an approach through the lower part of the chest necessitates reaching through the diaphragm to operate in the abdomen.

The approach that I am suggesting combines the thoracic approach with an abdominal approach. Adequate exposure is obtained by splitting the diaphragm. The incision is applicable for operations on esophagus, cardiac end of stomach, total gastric resections, diaphragmatic hernia, splenectomy, and vagus section when it is necessary to combine vagus section with gastroenterostomy.

The patient is placed on the table with the left side of the chest up, in a true lateral position. The position is similar to the position used for posterolateral approach to the thorax. Intratracheal anesthesia is used. The incision is made over the ninth rib and extends from the angle of the rib across the costal arch and for about 2 inches into the abdomen. This brings the incision to the lateral border of the left rectus sheath. The ninth rib is removed from its angle to the costochondral junction. The thorax is entered through the bed of the ninth rib. At this point the pulmonary ligament is divided so that the lung falls away from the diaphragm. The incision is then extended across the costal arch and for about 2 inches into the peritoneal cavity. The diaphragm is then split, starting at the point where the costal arch was divided and extending the split in the diaphragm to the esophageal hiatus. Rib spreaders are then placed between the eighth and tenth ribs posteriorly. By opening the rib spreaders very adequate exposure is obtained from the aortic arch in the thorax to the duodenum in the abdomen. As shown in Figure 1, the exposure of the esophagus, stomach, and spleen is entirely adequate for any operative procedure involving these organs. After completion of the operation, the diaphragm is sutured together with interrupted cotton mattress sutures.

In cases in which an esophagogastrectomy has been done, the diaphragm can be sutured to the gastric side of the anastomosis at any desired level, thus leaving the stomach as an abdominal organ, rather than transplanting it into the thorax. In such cases the phrenic nerve is crushed as it crosses the pericardium to prevent motion of the diaphragm postoperatively. After the diaphragm is sutured, the incision is closed with interrupted cotton sutures with underwater drainage.

Postoperative course of these patients has been entirely uneventful. They have been ambulatory after 48 hours.

This approach has the following advantages:

1. The exposure is more complete by this method than with either the abdominal or thoracic approach.

From the Surgical Service, University of Colorado School of Medicine.

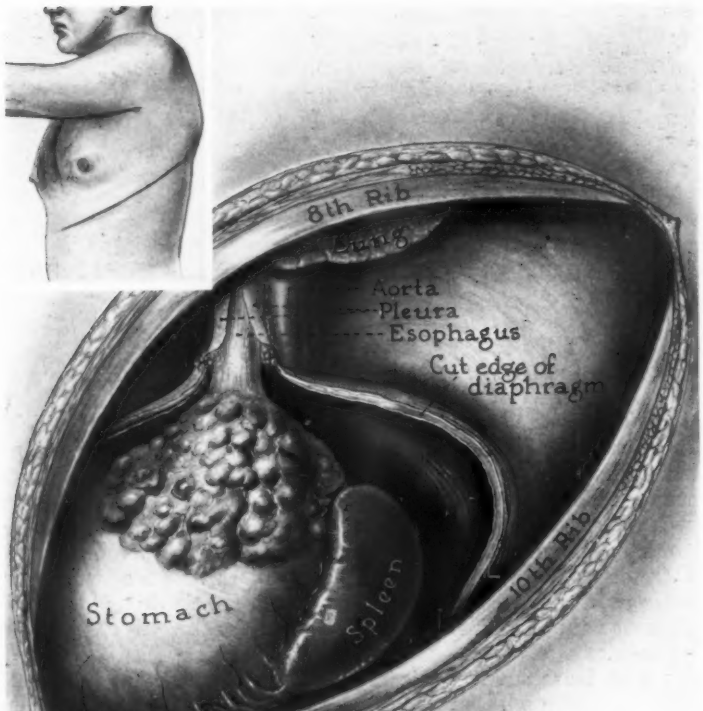

Fig. 1. Drawing illustrating exposure of organs through the thoracicoabdominal incision.

2. There is less danger of hemorrhage because the left gastric and the short gastric vessels can be divided under direct vision.

3. The diaphragm can be sutured at the desired level leaving the abdominal organs in the abdomen.

4. In the case of esophageal hiatus hernia, the sack can be completely removed and also the abdominal organs can be explored at the completion of the operation.

5. In splenectomy adhesions of spleen to diaphragm can be separated under direct vision thus avoiding the danger of hemorrhage.

6. The patient suffers less shock because the plane of anesthesia is much lighter than is necessary for abdominal incisions.

7. The operating ti.ne is decreased because of the better exposure.

8. The convalescence is shortened because there is less danger of wound disruption in thoracic than in abdominal wounds.

In conclusion, I have used this operation for carcinoma of the esophagus, total gastrectomy, splenectomy, and diaphragmatic hernias and have found the operation to be entirely satisfactory.

HISTOPATHOLOGY OF THE ANAL DUCTS

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IN 1880 Herrmann and Defosses noted in the anal regions of human embryos certain channels, lined with epithelium, which emptied into the anal crypts. These tubules, which occurred in simple and in branched forms, were seen at times to penetrate the fibers of the internal anal sphincteric muscle. Their lining of low columnar, dark-staining cells was distinctly different from the goblet cell investment of the rectum and the stratified squamous epithelial mantle of the anal canal. These pioneer investigators suggested the thesis that the tiny ductular "recesses" that they described might play a rôle in the initiation and spread of infection around the anus. The anatomic and embryologic aspects of their work were confirmed by Johnson, Lockhart-Mummery, Harris, Tucker and Hellwig, and Pope, to name a few. Lockhart-Mummery expressed the belief that these ducts were vestigial remnants of the sexual scent glands of lower animals but he could not ascertain their function in human economy. Observing that sometimes they terminated blindly in the ischiorectal fossa, he suggested that they were potential avenues for the lateral spread of anal infections.

Tucker and Hellwig remarked on the paucity of these ducts in the human subject as compared with the number found in certain lower animals. In a comparative embryologic study they detailed various modifications of the cells lining the ducts from the anus outward through the internal anal sphincter. They related the origin of certain anal fistulas to a primary infection in and about the anal ducts. In 1933 Pope described the presence of acinus-like buds in connection with the aforementioned structures. In 1936 Bremer noted the postnatal disappearance of secretory cells from the anal ducts in human beings. He observed that usually not more than eight such ducts are to be found in any one rectum. In the same year Morgan observed that most of the ducts had their orifices in the posterior portion of the anal canal.

Briefly then, columnar lined epithelial ducts (anal ducts) are reported to exist in certain lower animals and in man. Their connection with the anal canal, their course through the internal anal sphincter, and their blind termination reaching at times as far as the iliac fossa have placed them "under suspicion" as avenues of perianal spread of infection. The present study was undertaken with a view to verifying or disproving certain statements relating to the incidence, position, and significance of the anal ducts.

MATERIALS AND METHODS

The apparently normal anal canals of a number of human embryos and of one male stillborn infant were secured for study of the developmental aspects of the ducts. For comparative anatomic studies similar material was obtained from 10 monkeys. For the study of possible early inflammation in anal ducts of human adults, 100 specimens were selected in which removal of the rectum and anus had been performed because of sigmoidal or rectosigmoidal lesions. Finally the slides made during a previous study of 100 cases of cryptitis in the human subject were reviewed to check on the presence of associated anal ducts and their possible rôle in the spread of anorectal inflammation. In each instance blocks were selected so as to include the mucosa of the rectum as well as of the anus. In the case of the male stillborn infant serial sections were prepared from a block including the entire circumference of the bowel. In the case of the human embryos, sections were semiserial. With the rest of the material the blocks taken were sufficient in number to yield the desired information. All blocks of tissue were embedded in paraffin, sectioned in the usual manner, and stained routinely with hema-

Abridgement of thesis submitted by Dr. Kratzer to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in proctology.

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Fig. 1. Anal region of human embryo showing origin of anal duct in relation to anal crypt (hematoxylin and eosin, ×68).

Fig. 2. Same duct as shown in Figure 1. At this level the duct has penetrated the sphincter muscle (hematoxylin and eosin ×68).

toxylin and eosin. When demonstration of the presence or absence of mucus was necessary, the Galantha method of staining this substance was employed.

FINDINGS

A. Male stillborn infant (eight months). Serial sections of anorectal region. Detailed study of 429 consecutive transverse sections revealed a total of 5 ducts, 2 of which were located in the anterior and 3 in the posterior half of the circumference of the bowel. The upper 312 of these sections were made through the rectal mucosa and in these no anal ducts were found, indicating that the direction of their penetration was not upward. The next 117 sections all showed one or more ducts, the openings of which were seen to be located at the level of the anal crypts where the mucosa of the bowel showed stratification of low columnar epithelium. The lining of the ducts was similar to that of the crypts. From 1 to 5 ducts were visible in each of these 117 sections and on 24 occasions actual penetration of the internal anal sphincter muscle was found to have occurred. In 42 sections the distal portions of the ducts were seen beneath a mucosal mantle of stratified squamous cells, indicating that the direction of ductular growth was away from the mucosa and downward. Moreover, studies based on reconstruction showed their course to be irregular and even sinuous rather than direct, as was formerly believed. Definite lumina could not always be demonstrated, probably as a result of tangential sectioning. In one duct there was a suggestion of an acinus-like bud with a single layer of cuboidal epithelium. The lowest sections included perianal skin, showing sweat glands, some of these being of the apocrine type. However, these sweat glands were not easily confused with the anal ducts described previously. Rarely did the two types appear in the same section.

B. Study of human embryos. Seven human embryos varying in length from 1.5 to 14.5 centimeters were obtained and from 4 to 8 small blocks of tissue were removed from the anorectal region of each. Slides from these prepared and studied in the usual way revealed

TABLE I.—STUDY OF SIX ANAL CANALS, FROM HUMAN EMBRYOS TO DETERMINE POSITION OF THE DUCTS WITH REFERENCE TO THE ANUS

Sex	Number of ducts	
	Anterior half	Posterior half
Female	0	1
Female	2	5
Female	0	1
Male	0	1
Male	1	1
Male	2	3
Total	5	12

ductal structures similar in appearance and distribution to those described previously, in 3 cases, each from a fetus more than 10 centimeters in length. No acinar budding was observed (Figs. 1 and 2).

To check further on the efficacy of "random" sections as a means of determining the number and location of these anal ducts 6 additional human embryos (3 male and 3 female) were studied in a similar manner. However, in this latter series the locations of the blocks were oriented as to their position on the specimen, whether anterior or posterior. The entire circumference of the anorectal region was thus included in the blocks, which were then sectioned serially. Every twenty-fifth section was preserved, stained, and mounted for study. Results are shown in Table I. One to 5 ducts were found in the posterior segments in all 6 cases. In only 3 were ducts seen in slides from the anterior segments. No sex difference was observed in relation to incidence or location of anal ducts.

C. Study of anorectal regions of 10 monkeys. Tissues fixed in formalin were obtained from the anorectal regions of 10 monkeys. The animals in question had been killed in the course of experimental studies and they did not exhibit gross evidence of disease of the terminal portion of the bowel. From each specimen two blocks of tissue were removed for sectioning, one from the anterior and one from the posterior portion of the anorectal region. In each instance the level of the anal crypts was selected on the basis of the findings cited in the foregoing. From each block two sections were made, one being stained with hematoxylin and eosin, the other with a stain for mucus.

Fig. 3. Normal anal duct from an embryo. The section, which was taken near the blind extremity, shows a lining of several layers of cuboidal epithelial cells (hematoxylin and eosin ×395).

In 10 preparations from 5 of the animals anal ducts were not observed—a finding which does not surprise us considering the nature of the sampling. Ducts were observed in tissue from the remaining 5 monkeys. Proximally, as in the human material, these ducts were lined by 4 or 5 layers of transitional epithelial cells which appeared to be more like low columnar than squamous cells. Distally a double layer of cuboidal epithelial cells was noted. Penetration of the surrounding muscle was found to be present in 2 and absent in 3 specimens. In 1 case mild periductal inflammatory infiltration with lymphocytes was noted. No acini were found but the mucicarmine stain gave a positive reaction in isolated regions of each duct, confirming our assumption that the lining cells were entodermal rather than ectodermal. The ducts in each specimen numbered less than 5 with a 2:1 predilection for the posterior half of the anal canals.

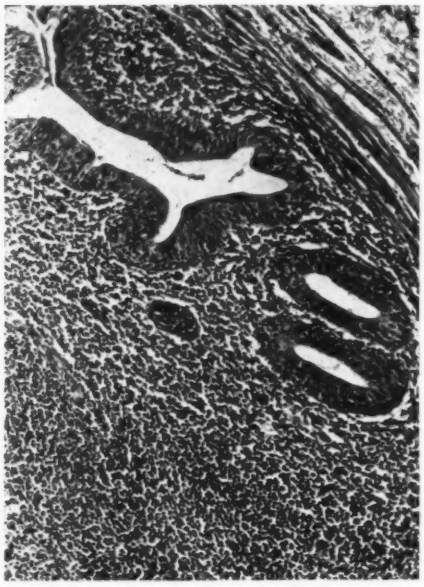

Fig. 4. Anal crypt showing cryptitis. The ducts are shown with the transitional type of lining seen usually at their orifices. Subacute periductal inflammation is present with many plasma cells (hematoxylin and eosin ×91).

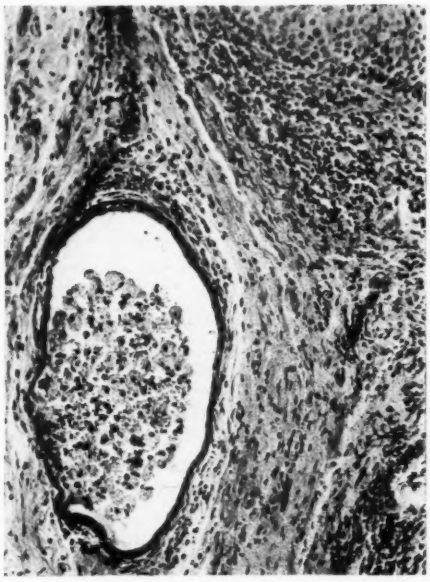

Fig. 5. Anal duct in an adult. The lumen is filled with polymorphonuclear leucocytes and débris. Around the duct may be seen a few lymphocytes and considerable scar tissue (hematoxylin and eosin ×127).

D. Histopathologic study of 100 normal (?) anal crypts from human subjects. These crypts were considered more or less normal even though the rectum and anus had been removed for carcinoma of the rectosigmoid. In any event no gross evidences of anorectal disease processes were present. From each specimen one block of tissue was taken in such a manner as to include an anal crypt. In the original material it was seldom possible to satisfy our desire to select a posterior crypt, inasmuch as "orientation" on the specimen was out of the question. However, taking this into account it was interesting to note that one or more ducts were demonstrated by *one* microscopic section in no less than 55 of the 100 blocks which had been sectioned for study. Serial sections no doubt would have shown a much higher incidence (Fig. 3).

For information relating to the origin and cause of these ducts, further sections were made on the 55 positive blocks and these sections were stained with hematoxylin and eosin and by the Galantha method for the demonstration of mucus. By means of this more or less random technique a definite origin of the anal ducts from a crypt was ascertained in 37 instances. In 33 slides the ducts were seen to penetrate the underlying muscle and a downward direction of growth was indicated in 22 sections wherein the epithelium overlying the deeper portions of the ducts was of squamous type. With minor variations the character of the epithelial lining of the ducts followed the pattern described in a foregoing paragraph. In 24 instances transitional columnar epithelium extended to the blind ends of the ducts. In 2 instances the proximal ends of the ducts were lined by stratified squamous epithelium. Results of staining for mucus were positive in 10 instances, the mucous cells appearing isolated or in small clumps scattered along the course of the ducts. No definite glandular acini were noted.

Of particular interest in this "normal" group was the presence in 13 cases of periductal inflammation. In 10 cases a chronic reaction was characterized by accumulations

TABLE II.—OBSERVATIONS ON 100 CRYPTS

	Cases	Per cent
Ducts not observed	45	45*
Ducts observed	55	55*
Showing ducts joining crypts	37	67.3†
Type of lining at entrance to ducts		
Squamous	2	5.4‡
Transitional	33	89.2‡
Columnar and transitional	2	5.4‡
Ducts penetrating muscle	33	60.0†
Type of lining of ampullae		
Transitional	24	72.7§
Columnar and cuboidal	2	6.1§
Cuboidal	5	15.1§
Columnar and transitional	2	6.1§
Situation in respect to type of lining of anal canal superimposed		
Squamous	22	40.0†
Transitional	33	60.0†
Showing periductal inflammation	13	23.6†
Associated with cryptitis	12	21.8†
Showing columnar epithelium	19	34.6†
Showing mucus with mucicarmine stain	10	52.6‖

*Per cent of 100.
†Per cent of 55.
‡Per cent of 37.
§Per cent of 33.
‖Per cent of 19.

of lymphocytes about the ducts, in 2 cases nests of plasma cells indicated the existence of a subacute inflammatory process and in 1 case an acute inflammatory reaction was noted with periductal accumulations of polymorphonuclear leucocytes and with edema of tissue. In no instance were the inflammatory cells located within the lumen of a duct. Cryptitis was associated in 12 of the 13 specimens in which there was periductal inflammation (Table II).

E. Review of some slides from cases of anal cryptitis incidentally showing anal ducts. In a previous study of 100 cases in which a gross diagnosis of cryptitis had been made, ductular structures had frequently been noted. This material was again restudied and 24 specimens were selected as being pertinent to the present investigation. Of these 24 specimens 9 showed definite microscopic evidence of active cryptitis, acute, subacute or chronic, as judged by the criteria outlined in section D. In 8 of these 9 cases an associated periductal inflammatory process of corresponding type was observed (Fig. 4). In 1 instance only did the inflammatory process seem to spread solely within the lumina of the involved ducts (Fig. 5). Two specimens showed periductal inflammation in the absence of cryptitis (Table III).

TABLE III.—REVIEW OF TWENTY-FOUR SLIDES SHOWING DUCTS TAKEN FROM CASES OF CRYPTITIS

	Cases	Per cent
Normal ducts	4	16.7*
Showing cryptitis	9	37.5*
Showing ductal or periductal inflammation	11	45.8*
Number of these associated with cryptitis..	8	72.7†

*Per cent of 24.
†Per cent of 11.

COMMENT

In order to understand the possible importance of the anal ducts as avenues for the spread of anorectal infection one must realize the fact of their existence. The present study emphasizes that fact. These ducts are few and small. When they appear in the "chance" section made from the anorectal region, they may seem to be insignificant tubules having no apparent connection with the anal mucous membrane. Yet, as has been shown, their peregrinations through the internal anal sphincter theoretically expose such remote locations as the ischiorectal fossae to the dangers of anal infection, through their lumina or their periductal lymphatics. Therein lies their main interest, since this and other studies have not attributed to them any useful function in man.

Their relation in point of origin to the anal crypts is perhaps of some significance from the standpoint of infection (1–3, 5, 9, 11, 14, 16).

In the present study periductal inflammation seemed to be definitely related to the coexistence of cryptitis. The discovery of cases wherein the crypts were normal and the ducts inflamed perhaps signified a condition of residual infection which had previously existed also within the crypts.

Are the anal ducts important in the production of anal fistula? The present study, while not answering this question, has per-

haps significantly confirmed the notion that the openings of the majority of the anal ducts lie posteriorly to the anus, in the zone where anal fistulas are prone to develop. This phase of the problem needs further investigation.

SUMMARY

The present study has amply confirmed previous observations that epithelium-lined ducts are to be found in monkeys, human embryos and human adults. Although few, they may be demonstrated rather easily in about 50 per cent of human anal canals. From openings in the anal crypts (most often posterior) they course outward and downward, often penetrating the internal anal sphincter. The majority are lined by transitional epithelium but definite mucus-producing cells may be demonstrated in 10 per cent of their linings. About 24 per cent of these ducts show, focally or diffusely, a periductal inflammatory reaction. When ducts are found in cases of anal cryptitis this incidence of periductal inflammation reaches 89 per cent. These ducts, we feel, provide possible pathways for the lateral spread of such periductal infection once the latter is established, and it is conceivable that ischiorectal abscess might have such a pathogenesis. Equally possible etiologically is the development of anal fistula, the predilection of which for the posterior portion of the anus corresponds to the principal site for the openings of the anal ducts.

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EXTRA-ARTICULAR REPAIR FOR RUPTURED COLLATERAL AND CRUCIATE LIGAMENTS

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ANATOMY

THE cruciate ligaments of the knee are two intra-articular ligaments that stretch between the tibia and femur, and cross each other between their attachments. The anterior cruciate ligament extends obliquely upward and backward from the space in front of the intercondylar eminence of the tibia to the back part of the medial side of the lateral femoral condyle. The posterior cruciate ligament passes from the back of the tibial spine forward and inward to the intercondylar surface of the medial femoral condyle. The anterior ligament prevents the tibia from being displaced forward on the femur. The posterior ligament prevents backward displacement of the tibia on the femur. Both cruciate ligaments are fairly tense in all positions. The anterior is under more tension with extension of the knee, while the posterior has increased tension with the knee in flexion. They act jointly to prevent anterior and posterior displacement of the tibia and also to limit the rotation of the tibia that occurs with flexion of the knee.

PHYSIOLOGY

The action of the cruciate ligaments is dependent on the action of the muscles that control the knee, and also to a great extent on the presence of satisfactory collateral ligaments. The cruciate ligaments act as check ligaments and work in conjunction with the collateral ligaments. They are dependent on the action of the quadriceps femoris muscle to give stability to the knee joint. A tear of the anterior cruciate ligament is not necessarily attended by loss of stability of the joint. A torn cruciate ligament has been established at operation without any instability of the joint. Studies on the cadaver have shown that the cruciate ligament may be divided without disturbance of function. However, a torn cruciate ligament in the presence of a weak quadriceps femoris muscle will show some instability of the knee joint, and lateral and posterior instability of the knee is always present when the tibial collateral ligament is divided along with division of the anterior cruciate ligament.

MECHANICS OF TRAUMA

The anterior cruciate ligament is torn as the result of abduction or hyperextension of the knee. When sufficient force is exerted to rupture the cruciate ligament, the tibial collateral ligament is also torn. The characteristic finding of a torn anterior cruciate ligament is the so called "drawer sign"; with the knee flexed, the tibia can be displaced forward on the femur. At the same time, the force could result in a tear of the medial meniscus, and more extensive involvement would include a depressed fracture of the outer tuberosity of the tibia.

It is not uncommon to overlook the tear of a cruciate ligament, because of the recognition of the more obvious injury to the medial meniscus and the fracture of the tibia. The tear of the quadriceps fibers is apparent in those cases where an exploration is made to repair the tibial collateral ligament. The torn muscular fibers may be in the deeper part of the muscle. The tear of the posterior cruciate ligament occurs when the tibia is forcefully displaced backward on the femur, tending to cause a posterior dislocation of the joint. The clinical sign is the excessive backward mobility of the tibia on the femur. The posterior cruciate may be torn without serious injury to a collateral ligament, and frequently there is no disability.

CONSERVATIVE TREATMENT

The treatment of a rupture of the cruciate ligaments is dependent on early recognition. If the joint is immediately immobilized in extension with the torn fibers intact, they can unite. In case the anterior cruciate is torn

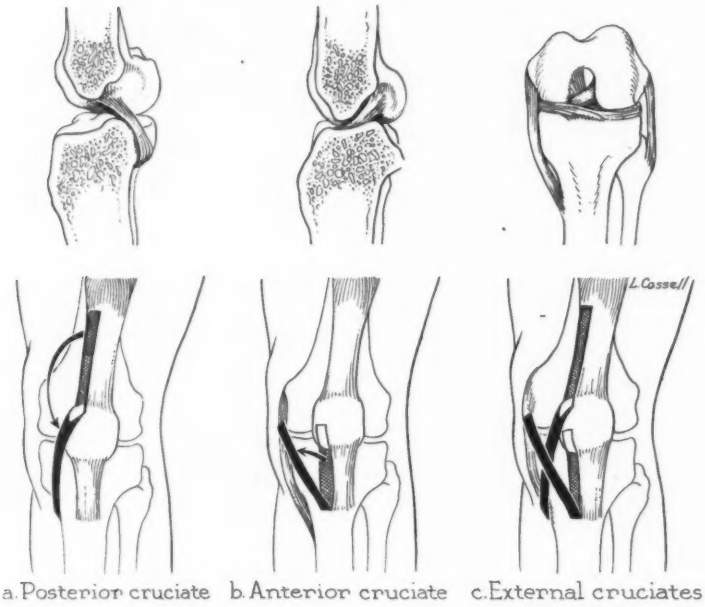

Fig. 1. Diagrammatic sketch comparing normal ligaments to reconstructed ligaments of the knee.

with the knee slightly flexed, the tibia is pushed backward and a cast is applied from the groin to the toes. Where the posterior cruciate ligament is torn, the tibia is pulled forward on the femur and the extremity is fixed with a plaster of paris cast. The fixation should be retained for 2 to 3 months. Exercises of the quadriceps femoris are started immediately.

When a collateral ligament is torn, fixation will allow healing. In those cases in which the meniscus is involved, removal of the ruptured meniscus should be carried out and the torn tibial collateral ligament repaired at the same time. In the case of a depressed fracture of the tibia, adduction and compression should be carried out in an attempt to reduce the fracture. Here again, fixation in extension by means of a cast to allow healing of the ligament is essential. Early activity of the quadriceps femoris must be urged and the return of normal function and active weight bearing instituted as soon as the symptoms have subsided. Where there are symptoms of instability or if the quadriceps is weakened, rehabilitation of this muscle will often give stability to the knee. In cases where the tibial collateral ligament is not repaired the disability can be great.

OPERATIVE TREATMENT

Many operations have been devised to reconstruct cruciate ligaments from fascia and tendons. The results of intra-articular operations have not been entirely satisfactory. Watson-Jones reports recurrences after time has elapsed. This is a difficult procedure at best. It can hardly be expected that the repair of the cruciate ligaments would give a satisfactory result where the tibial collateral ligament remains ineffective. On the other hand, a simple repair of the tibial collateral ligament does not always result in relief of the symptoms when the cruciate ligament is also torn (Campbell). Since the tibial collateral ligament has been torn and stretched over a long period of time, the structures are very weak; therefore, a shortening of this ligament after the manner of Mauck would not be adequate, and supplementary tissue is necessary.

Fig. 2. A, Anteroposterior view of anatomical subject with division of tibial collateral and cruciate ligaments showing separation of the medial condyle from the tibia. B, After tendon transplant, showing decrease in the gap between the tibia and the medial condyle. C, Lateral view of anatomical subject with division of the tibial collateral and cruciate ligaments, showing posterior displacement of tibia on femur (positive "drawer sign"). D, After tendon transplant, showing normal relationship between tibia and femur with attempt to displace the tibia posteriorly on the femur (negative "drawer sign").

AUTHOR'S METHOD

The tendon of the quadriceps femoris offers a tissue that is strong and easily obtained, and one of its attachments may be retained. A strip ½ inch wide and about 2½ inches long is made from the medial side of the tendon of the quadriceps femoris (Fig. 1, a). The proximal end is divided. The distal attachment is dissected so that it remains attached only to the upper end of the patella. The proximal end is then reflected downward and attached on the medial and posterior side of the tibia. In this way a strong, fibrous band passes obliquely from the anterior part of the knee at the level of the condyle to the posterior part of the tibia in the same direction, and has the same effect

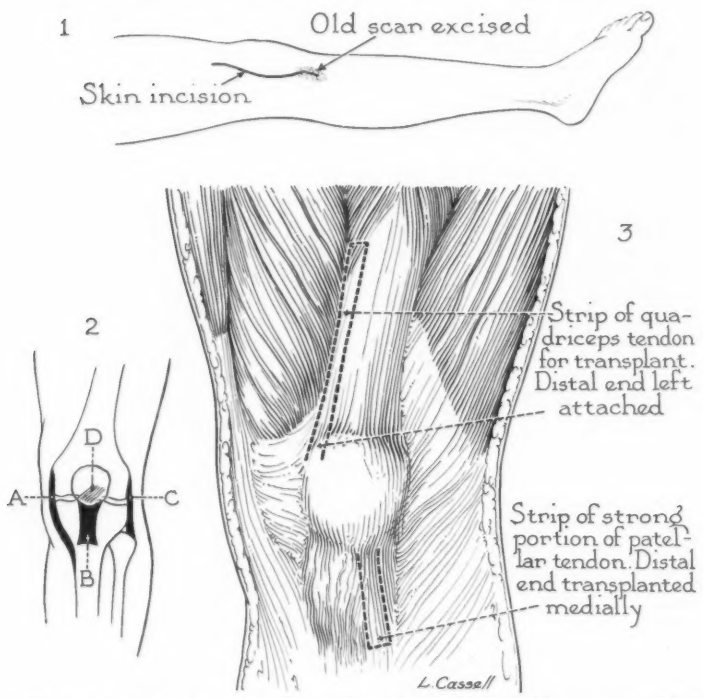

Fig. 3. 1, Scar of previous operation, and author's incision. 2, Diagrammatic sketch of the ligaments of the knee. *A*, Medial collateral ligament; *B*, Ligament of the patella; *C*, Tibial collateral ligament; *D*, Cruciate ligaments; (In this case *A* and *D* were torn.) 3, Drawing showing the source of transplants.

as an anterior cruciate ligament except that in this case it is outside the joint. It also is a strong ligament on the medial side of the knee, re-enforcing the tibial collateral ligament. The transplant is fastened directly to the bone through an incision in the periosteum; the periosteum is turned back by means of an osteotome and direct contact is thus obtained between the transplant and the bone. The attachment can be made by using a nail, or still better, a staple. The ligament is held in place by means of mattress sutures of chromic No. 1 catgut passed from the periosteum through the transplanted part of the tendon. A good stable ligament is thus obtained.

In cases of severe tears, further repair may be made by transplanting part of the ligament of the patella (Fig. 1, b). A ½ inch strip is made from this ligament on the medial side. This is dissected free and separated from its attachment to the patella. The proximal end of the ligament is then transplanted posteriorly in the region of the medial surface of the lower end of the femur, and attachment is made to the fascia in this area. The ligament of the patella has the advantage that it runs in the direction (see illustration) of the anterior cruciate ligament, and at the same time acts to further re-enforce the weakened tibial collateral ligament.

A torn collateral ligament, when not repaired, gives a weakened structure on the medial side of the knee, and at the same time it prevents the function of the quadriceps femoris muscle in that area. The repair by a transplant from the tendon of the quadriceps femoris restores a functional attachment for the quadriceps femoris and activates the muscle in this area. The increased strength of the quadriceps is important in the restoration of

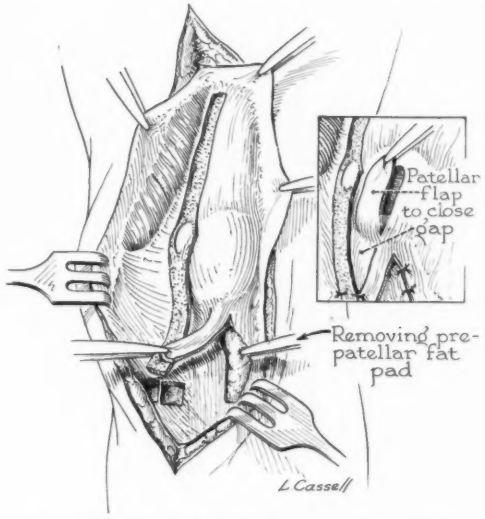

Fig. 4. Transplant from the tendon of the quadriceps femoris muscle and the ligament of the patella. Inset—shows source of fascia to cover gap.

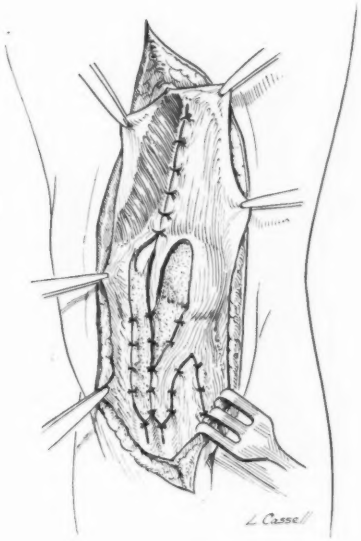

Fig. 5. Suturing.

function. In addition, the transplant from the tendon of the quadriceps femoris muscle tends to activate the entire quadriceps muscle. The medial side of the muscle, when the tibial collateral ligament is torn, loses its function and becomes weak and powerless. With the repair by means of the tendon transplant the quadriceps' power is restored and this increase in strength tends to stabilize the knee. The third advantage of this type of repair for a torn cruciate ligament is its oblique direction. The direction of the new ligament on the external surface of the knee is the same as that of the anterior cruciate ligament within the knee, and thus acts as a check against excessive mobility. As can be seen from the illustration (Fig. 1, c), when the transplant from the tendon of the quadriceps femoris is in position and the transplant from the ligament of the patella is brought upward and posterior, the ligaments cross to form a cruciate ligament on the external surface. This is suggestive of the action of the ligament, but for clinical purposes it is more important that the repair of the tibial collateral ligament be emphasized. Next in importance is the increase in the ability to restore normal strength to the extensor muscles of the knee. The operation is technically simple, is extra-articular, and excellent results have persisted.

In carrying out this procedure on an anatomical subject for demonstration we saw how a knee with definite instability which permits excessive abduction and internal rotation, and also has a positive "drawer sign," was converted into a stable knee (Fig. 2, A and C). There was no possibility of abduction or excessive rotation, nor displacement of the tibia, after the ligament had been transplanted (Fig. 2, B and D).

These principles for the torn cruciate ligament have been applied to 15 cases which have come under my observation. In the early cases of a torn tibial collateral ligament and a torn cruciate ligament, fixation of the knee in extension with a plaster cast was carried out. Exercise for the quadriceps muscle was started immediately; weight bearing was started as soon as was possible without pain. The removal of the cast was followed by exercises of the extensor muscles of the knee. The patient was not permitted to return to work until the extensor group could carry out normal function. In this way instability and later develop-

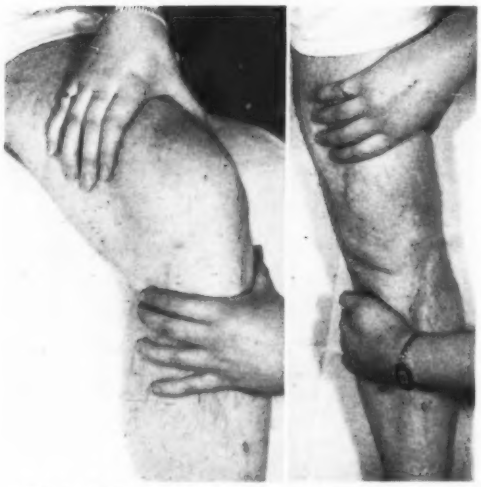

Fig. 6. a, left, Showing anteroposterior stability of the knee, with action against resistance. b, Showing lateral stability of the knee, with action against resistance.

ment of arthrosis of the knee were prevented. In the early cases that required surgery, the torn collateral ligament was repaired. In the older cases, where there was very little instability but an uncertainty and a "drawer sign" with the knee relaxed, exercises for rehabilitation to full strength of the quadriceps muscle were sufficient to restore normal function and cure the cause of the patient's complaints. Where there was instability and signs of a definite tear of the tibial collateral ligament, surgery was advised. Since this latter type of case is most difficult and most important, a case report is included.

REPORT OF CASE

The patient was a 43 year old businessman who complained of pain, weakness, and swelling in the left knee, with disabling instability. He had injured his knee in a plane crash during the first World War, and it had been getting progressively worse. When he came to me there was disability to the extent that it interfered with his occupation as the owner and manager of a dry goods store. After the injury the knee kept troubling him, and in 1920 after a diagnosis was made of a fractured medial meniscus he was operated upon and the meniscus was removed. He was relieved until 1927, when the symptoms recurred and he began to have locking, again with instability of the knee, as well as pain and swelling. He was operated upon the second time and the lateral meniscus was removed. Some improvement followed this until 1930, when there was a recurrence of a great deal of instability. He could not play golf, and he was unable to take part in other sports. After prolonged standing the knee would swell and become painful. An attempt to swing a golf club or to bring the knee into a rotary position caused a feeling of the knee slipping out of joint (subluxation). The knee became swollen and remained so. He was re-examined by the surgeon who removed the cartilage and was told that he had a torn cruciate ligament with instability of the joint. He was advised against an operation for repair of the cruciate ligaments since, in the surgeon's experience, such surgery had been unsuccessful. He was told to bandage his knee and to avoid strain, and if the knee continued to get worse the best treatment would be an arthrodesis of the knee.

General examination of the patient showed that he was normal in every way, with the exception of the knee. His blood pressure was 100/65 and his laboratory tests were normal. Physical examination of the knee showed definite instability. The leg could be brought out into valgus at an angle of about 40 degrees, when the knee was slightly flexed. With the knee flexed and the foot brought into external rotation, any attempt to put weight on the knee caused a definite subluxation. The tibia could be drawn forward as well as pushed posteriorly on the femur (positive "drawer sign"). There was definite synovial thickening and increased fluid. The fat pad was palpable and thickened.

Diagnosis was made of a torn cruciate ligament, as had been expressed by the original surgeon. The chief difficulty was the instability of the knee due to the weakened tibial collateral ligament. Surgery was advised.

At the time of operation the tibial collateral ligament was exposed and in some areas was found to be as thin as paper. The medial side of the ligament of the patella was frayed out, stretched, weak and ineffective. A transplant was taken from the tendon of the quadriceps femoris muscle and carried obliquely and posteriorly over the medial side of the knee to be fastened on the tibia directly into the periosteum (Fig.3). A second transplant was then taken from the ligament of the patella. In removing the transplant from the ligament of the patella, the prepatellar fat pad was exposed. It was found to be hypertrophied and showed signs of chronic inflammation, and it was removed through this opening. The transplant of the ligament of the patella was freed distally and the proximal part was allowed to remain attached to the patella. The distal part was transferred and attached to the tibia (Fig. 4). In this case digression from the proposed operation was adapted to meet the extraordinary weakness of structure present on the medial side of the knee. With the new ligaments in place, there was still a weakness of the structures between the two ligaments. Adequate fascia to cover this gap was obtained from the anterior part of the patella (Fig. 4, insert). A flap of aponeurosis was reflected and placed between the

ligament made from the tendon of the quadriceps femoris muscle and the one made from the ligament of the patella. The ligaments were sutured with No. 00 chromic catgut. The attachments to the periosteum were held in place with chromic No. 1 catgut (Fig. 5). The result was a firm collateral ligament which prevented the knee from any abnormal lateral movement. In addition, the transplant from the tendon of the quadriceps femoris brought into play fibers of muscle which previously were not effective. Furthermore, the pull on the newly formed collateral ligament was in the direction of the posterior cruciate ligament so that posterior displacement of the tibia on the femur was not possible. The skin was closed with black silk, in the usual manner, and a compression bandage was applied. The fifth day after operation quadriceps exercises were started. He had an uneventful convalescence. His temperature rose to 99 degrees the first 2 days and then became normal and remained so. The sutures were removed on the twelfth day, and he was up in a chair 2 days later. On the twentieth day he was walking, and he left the hospital on the twenty-fourth day. The exercises were continued, to increase the strength of the quadriceps. He returned to work after 2 weeks and continued his exercises. When seen 4 months after operation he was able to come to a squat position with all his weight on the leg operated upon. He was able to play golf and has continued his occupation without any return of symptoms. When last seen 2 years after operation, he still had complete recovery without any sign of recurrence. The knee was normal in size and appearance, and firm, strong fibrous bands were palpable under the skin. The knee was stable and he was able to do all his work without symptoms (Fig. 6).

SUMMARY

1. The symptoms of a torn cruciate ligament are dependent on the strength of the collateral ligaments, as well as on the effectiveness of the quadriceps femoris muscle.

2. Torn cruciate and collateral ligaments will respond to early efficient conservative treatment.

3. Neglected cases of torn cruciate ligaments with weak, stretched collateral ligaments, require surgical repair. For these cases an extra-articular method of repair has been devised.

4. The author's operation is described. A section of tendon of the quadriceps femoris muscle is taken and division is made proximally, the distal part being left attached to the patella. The proximal end of the section of tendon is then fastened to the posterior part of the upper end of the tibia. A section of the tendon of the patella about a centimeter in width can then be separated leaving the distal end attached. The free proximal end can then be transferred obliquely to be attached in the region of the condyle of the femur posteriorly. We thus have an extra-articular cruciate ligament. More important is the fact that we have reconstructed a firm, strong collateral ligament.

ANATOMIC DISARTICULATION OF THE HIP

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IN order to obtain an ideal stump which will close without tension and minimize shock incident to disarticulation at the hip joint, a technique has been developed by which the dissection proceeds along fascial planes and the muscles about the hip are divided at either their origins from the pelvis or their insertions into the femur.

This technique is in accord with principles advocated by Callander and Kirk. Callander has found that, for amputations just above the knee, detachment of the muscles from their insertions or at their points of origin is much less shocking than amputations through the muscles of the thigh. Kirk, in describing amputations at the hip, states: "All muscles except those normally belonging in the buttocks are removed from the stump, saving one muscle flap, which is conserved to fill up the acetabulum if a disarticulation is elected. The muscles on the whole are cut at their origins."

In the operation to be described, detachment of the muscles from their origins or insertions permits closure of the wound with ease and without tension. The large gluteal flap forms an excellent stump. A familiarity with the anatomy of the structures about the hip joint is essential.

This operation has been performed by members of the staff of the Campbell Clinic on 7 patients, and has been employed successfully in one additional case by Dr. Van Domselaar in Buenos Aires.

Technique. The extremity is elevated and, unless contraindicated, an elastic bandage is applied to express as much blood as possible from the leg and thigh into the systemic cir-

From the Willis C. Campbell Clinic.

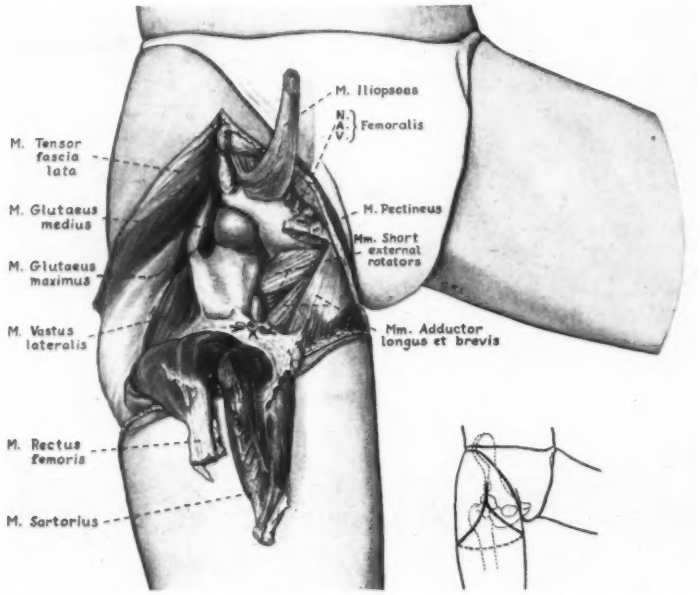

Fig. 1. The stage of the anatomic disarticulation following ligation of the femoral vessels and nerves, and detachment of the sartorius, rectus femoris, pectineus, and iliopsoas muscles. Inset shows the line of the incision.

culation. The bandage should not be wrapped over a malignant tumor, as cells from the neoplasm might be forced into the general circulation. An Esmarch tourniquet is applied tightly about the extremity, 2 inches below the level of the disarticulation. Unless the tourniquet is placed below the point of amputation, the limb will refill with blood during the operation despite primary ligation of the femoral artery and vein, the blood coming through the anastomotic branches of the inferior gluteal artery with the medial femoral circumflex and highest perforating arteries.

The patient is placed on the unaffected side and, after the routine surgical preparation, sterile drapes are so applied as to permit free movement of the extremity.

A racquet type of incision is employed. Beginning at the anterior superior iliac spine, the incision is curved downward and medially almost parallel with Poupart's ligament, to a point on the inner aspect of the thigh 5 centimeters below the origin of the adductor muscles. Before proceeding farther, the femoral artery and vein are isolated and ligated and the femoral nerve is injected with novocain and divided. The incision is then continued around the posterior aspect of the thigh approximately 5 centimeters distal to the ischial tuberosity, and along the lateral aspect of the thigh about 8 centimeters distal to the base of the greater trochanter. From this point, it curves upward, joining the original incision below the anterior superior iliac spine (insert, Fig. 1). The sartorius muscle is now detached from its origin at the anterior superior iliac spine and reflected distally, the rectus femoris is detached from the anterior inferior iliac spine and also reflected distally, and the

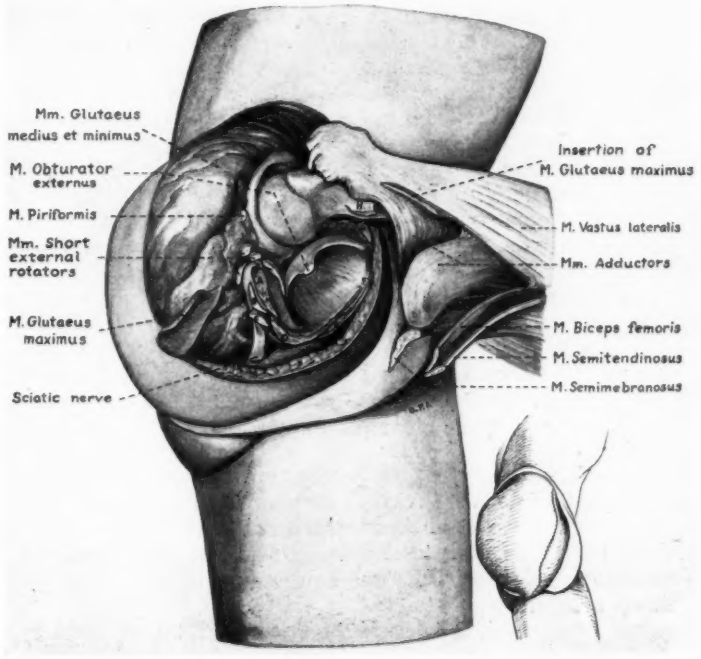

Fig. 2. The stage of the anatomic disarticulation following separation of the glutei from their insertions, division of the sciatic nerve, severance of the short rotators, and detachment of the hamstring muscles from the ischial tuberosity. Insert shows the stump after closure of the wound.

TABLE I.—ANATOMIC DISARTICULATION OF THE HIP

Patient No.	Age Years Sex	Diagnosis	Date of Operation	Result
J.D. 55300	40 M	Osteogenic sarcoma lower 3rd of femur	2-16-42	Died* Dec., 1942
E.M.H. 55311	15 F	Osteogenic sarcoma lower 3rd of femur	2-26-42	Died* June, 1942
H.H. 55737	34 F	Osteogenic sarcoma middle 3rd of femur	4-20-42	Died* June, 1942
H.J.O. 53421	48 M	Charcot hip with secondary infection	8-18-42	Living
Z.B. 59340	19 F	Fibrosarcoma right thigh	12-15-42	Living
E.S. 60000	14 F	Osteoblastic osteogenic sarcoma lower 3rd of femur	6-25-43	Died* Nov., 1943
K.L. 67448	58 M	Fibrocystic disease left femur	12-15-45	Living

*Died with metastasis

pectineus is divided approximately ¼ inch from the pubis. By externally rotating the thigh, the lesser trochanter is brought into view. The iliopsoas tendon is then severed at its insertion and reflected upward (Fig. 1). The adductor and gracilis muscles are next detached from the pubis, and that portion of the adductor magnus which arises from the ischium is severed at its origin. The plane between the pectineus and the obturator externus and short rotators is delineated and the branches of the obturator artery are ligated. The obturator externus muscle is later detached from its insertion into the femur; if the muscle is divided at its origin, the obturator artery may be severed and retract into the pelvis, resulting in hemorrhage difficult to control.

The thigh is now rotated internally and the gluteus medius and minimus muscles are detached from their insertions into the greater trochanter, and retracted upward. The fascia lata is divided below the insertion of the tensor fasciae latae muscle in the line of the skin incision, together with the lowermost fibers of the gluteus maximus muscle, and the tendon of the gluteus maximus is separated from its insertion into the linea aspera and retracted upward. The sciatic nerve is next injected with novocain and divided. The short rotators, of the hip, i.e., the pyriformis, gemelli, obturator internus, obturator externus and quadratus femoris are divided at their insertions into the femur, and the hamstring muscles are then severed from the ischial tuberosity (Fig. 2). The disarticulation is now complete except for incision of the capsule of the hip joint near the acetabulum, and division of the ligamentum teres.

From the description given, it will be observed that all the muscles are divided *close to the bone*, at either their points of origin or insertion, and that the dissection proceeds along the fascial planes. All the arteries are clamped and ligated as they are encountered. Excessive bleeding during the operation is prevented by the initial ligation of the femoral artery above the profunda. The other major vessels which require ligation are the branches of the obturator artery and the inferior gluteal artery.

The disarticulation having been completed, the gluteal flap is brought forward and the distal portions of the gluteal muscles are sutured to the points of origin of the pectineus and adductor muscles. The skin is closed in the routine manner. The gluteal flap is sufficiently large to permit closure without tension (insert, Fig. 2). A drain is placed in the inferior portion of the incision, to be removed after 24 to 36 hours.

Five of the 7 operations performed by this method were for malignant tumors of the femur, 1 was for a Charcot hip with a secondary infection, and 1 was for a fibrosarcoma of the thigh. There were no operative deaths. Four of the patients died of metastases from 2 to 10 months later (Table I).

These same principles have been followed in disarticulation of the shoulder. The deltoid muscle was detached from its insertion and retracted upward, and the other muscles about the joint were severed at their attachments to the scapula or humerus. It was unnecessary to divide any of the muscles through their bodies. The deltoid flap fell into place, permitting an ideal closure without tension.

CONCLUSIONS

Disarticulation of the hip is, at best, a shocking procedure. It should not be undertaken unless blood is available for transfusion during the operation. Experience indicates that the method presented is accompanied by

less shock than the conventional type of disarticulation of the hip. Dissection is carried out along fascial planes, permitting the surgeon to isolate and clamp the vessels as they are brought into view. Detachment of the muscles in avascular areas, i.e., at their origins or insertions, is a major factor in the prevention of excessive blood loss. The procedure is a little more time-consuming than those in which the muscles are divided through their bodies, though the expenditure of the additional time is well justified by the better postoperative condition of the patient.

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THE ADVANTAGES AND LIMITATIONS OF THIOURACIL THERAPY IN THYROTOXICOSIS

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WHEN thiouracil was introduced by Astwood and other pioneer workers in this field, the possibility seemed definite that no longer would there be need for surgical therapy in hyperthyroidism. However, experience with the drug has revealed enough limitations to leave iodine a definite place in the treatment of hyperthyroidism. Nevertheless, the introduction of thiouracil and allied compounds can be considered epochal in the treatment of hyperthyroidism. Since several compounds are known to exert the same action on the thyroid as does thiouracil, it is of course likely that other drugs will be found which will be superior.

Reactions. The reactions sustained by the patient during treatment with thiouracil represent one of the greatest disadvantages of the drug. In a study of 1,543 cases reviewed from the medical literature, reactions were noted in 13.8 per cent of patients treated. The most serious reaction was agranulocytosis, which was encountered in 0.78 per cent of patients in the series reviewed. Although much less serious, leucopenia was more common, being reported in 3.11 per cent. Vomiting, dermatitis, and pruritis were encountered in 2.9 per cent, 1.1 per cent, and 4.5 per cent, respectively. A great variety of other reactions, including purpura, localized edema, arthralgia, swelling of the salivary glands, etc., have been observed. The mortality rate, which in the series of 1,543 cases was 0.45 per cent and is as great as that in thyroidectomy for moderately toxic goiter, would indicate a most serious disadvantage or limitation in the use of thiouracil.

In our series of 79 cases the reactions were similar but slightly higher in incidence than were those reported in the literature (Table I), although most of the reactions were relatively insignificant. We encountered no cases of agranulocytosis, although marked leucopenia developed in 4 cases.

We noted very little correlation between dosage and duration of drug therapy although the most serious reactions were apt to occur early in treatment. It must be remembered, however, that agranulocytosis may develop at any time during the course of therapy. No death in our series could be attributed to thiouracil. One death occurred while the patient was being treated with the drug, but a pharyngeal abscess and pneumonia seemed to account for the fatality without thiouracil being considered as a complicating factor. This patient did not have agranulocytosis, leucopenia, or bone marrow changes.

Advantages and indications for the use of thiouracil. In our estimation, thiouracil has its greatest usefulness in the treatment of moderately severe toxic goiter in patients who are so toxic that preparation with iodine will not lower the hyperthyroidism to a degree sufficient to allow bilateral thyroidectomy safely. Thiouracil likewise is strongly indicated in patients who have cardiac failure secondary to hyperthyroidism as seen most commonly in toxic nodular goiter. Treatment over a period of several weeks invariably results in improvement of the cardiac status; the nutritional state likewise improves remarkably. In recurrent goiter and in mildly toxic goiter, with a small gland, permanent remissions are obtainable in a large percentage of cases. In patients who are sensitive to iodine or have tuberculosis (in which disease iodine is supposedly dangerous) thiouracil is strongly indicated.

Disadvantages and limitations in the use of thiouracil. The greatest disadvantage in the use of thiouracil is obviously the mortality rate produced by administration of the drug. Although we have not had any fatalities in our series which could be attributed to the use of the drug, the mortality rate in the 1,543 cases

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TABLE I.—TOXIC REACTIONS IN 79 CASES TREATED WITH THIOURACIL AT ILLINOIS RESEARCH HOSPITAL

	Cases
Pruritis, rash	8
Severe leucopenia	4
Edema	1
Arthralgia	1
Nausea and vomiting	2
Submaxillary swelling	1
	17 or 21 per cent

Reactions were sufficiently serious to require cessation of the drug in 9 per cent.

reviewed (3) in the medical literature was 0.45 per cent. This one disadvantage is so serious that the drug can probably never be used with utter safety, particularly since it is now being used with great care and only by a relatively few workers, most of whom are making such a careful study of the drug that reactions are detected early. Even though the incidence of other reactions was 13.8 per cent, most of them can be considered as insignificant. The action of thiouracil is so slow that it literally takes weeks to eliminate the thyrotoxicity. This delay might be considered uneconomical and many patients as well as physicians may become impatient, particularly since thyroidectomy can be performed in the mildly toxic goiter patient, with a very low mortality rate and with only 12 to 15 days of preliminary iodine therapy. In the presence of crisis the drug is dangerous and should not be given, particularly since in this group of patients the effect is so slow that it would probably not decrease the mortality rate. Thiouracil produces increased vascularity of the thyroid gland, thereby making the operation more difficult because of the additional hermorrhage encountered. The use of iodine for 10 to 12 days before operation, however, eliminates or minimizes this vascularity. Thiouracil does not produce a decrease in the size of the gland. Accordingly, in toxic nodular goiter, if the action is optimal and sustained, so that operation is not indicated, we still have to be concerned about the possibility of the development of carcinoma. The high incidence in a goiter belt of carcinoma in nodular goiter has been noted in a previous publication (2) and made the authors concerned as to the fate of patients with residual nodules after thiouracil

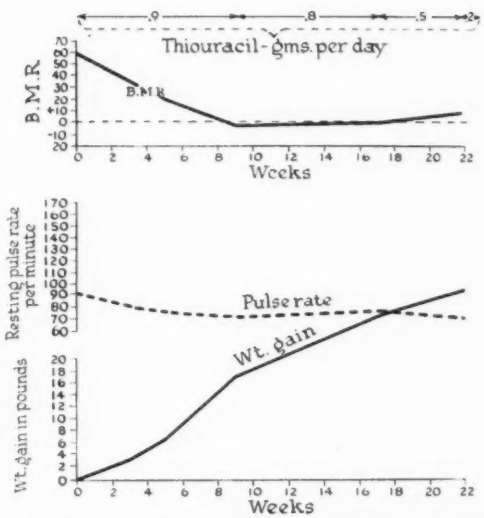

Fig. 1. Average response of hyperthyroidism to thiouracil. The basal metabolic rate was reduced from 60+ to 0 in 8 weeks, representing a drop of about one point in the metabolic rate for each day of therapy.

therapy. We have not, however, encountered any carcinomas in glands of patients treated with thiouracil and know of no such instances in the literature; therefore we are of the opinion that the possibility of development of such a complication can be considered insignificant.

Dosage and response to thiouracil. We are using a dosage of 200 milligrams three times a day. The drug is maintained at this level for at least a few weeks and then dropped to one-third to one-half of this amount, depending upon the response of the patient. The patient must be watched at all times and leucocyte counts performed two or three times a week. Moreover the patient must be instructed to report all reactions regardless of severity or degree. Since severe reactions including severe agranulocytosis can develop at any time,

TABLE II.—INDICATIONS OR ADVANTAGES OF THIOURACIL

1. Patients so toxic thyroidectomy not safe with iodine.
2. Mild toxicity with small gland. (Permanent remission in about half of this group.)
3. Recurrent thyrotoxicosis (following operation) with small gland.
4. Thyrocardiacs.
5. Patients sensitive to iodine or having pulmonary tuberculosis.

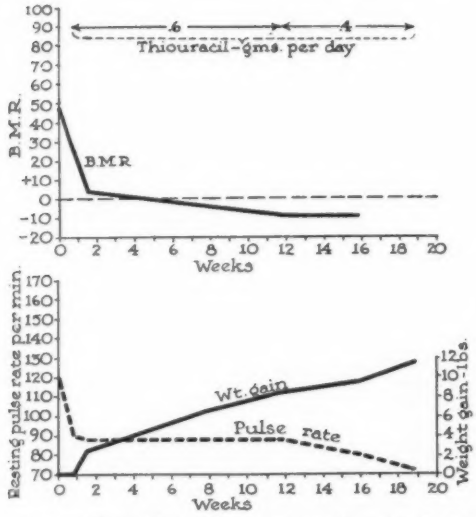

Fig. 2. Unusually rapid response to thiouracil which is perhaps explained for the most part by inaccuracy of the initial basal metabolic reading.

the fact that administration of the drug for 4 to 5 weeks has not resulted in reactions cannot be considered as an excuse for less critical observation. The danger of development of agranulocytosis is so unpredictable that the drug should be discontinued for 3 or 4 days before operation lest agranulocytosis develop on the day of operation and not be detected.

Reference has already been made to the desirability of giving iodine as Lugol's solution or iodide for 12 to 14 days preceding operation. This program will result in a great decrease in vascularity, and the operation is thereby made much easier.

Lahey and others have noted that there is regression of hyperthyroidism during thiouracil therapy to a degree equal to about one point in basal metabolic rate for each day of

TABLE III.—LIMITATIONS OR DISADVANTAGES OF THIOURACIL

1. High mortality rate (0.45 per cent in 1543 cases—Fowler)
2. Toxic reactions 13.8 per cent.
3. Slow action (uneconomical).
4. Useless in crisis (dangerous?)
5. No decrease in size of gland. (If remission permanent, is persistent gland dangerous—Carcinoma?)
6. Increases vascularity of gland,—thus adding to operating time and blood loss unless iodine is given.

TABLE IV.—RESULTS AFTER DISCONTINUATION OF THIOURACIL

No. of Cases	Average initial BMR-70	Average duration thiouracil—mos.	Remission?
10	65.3	7.5	No. Symptoms recurred in 1 to 7 mos.
9	29.1	6.8	Yes. 8–17 mos since thiouracil discontinued.
7	51.7	6.4	Yes. But only 1–5 mos. since drug discontinued.

BMR. Basal metabolic rate.

treatment. In an analysis of our patients, we noted, however, that it took a period slightly longer than this to bring the patients to a normal basal metabolic rate. In our patients with toxic diffuse goiter it took an average of 8.8 days in addition to the one day per point of basal metabolic rate, to bring the rate to normal. Patients with toxic nodular goiter respond somewhat more slowly than do those with toxic diffuse goiter. For example, in the toxic nodular group, it took an average of 28.5 days longer than the one day per point of basal metabolic rate for return to a normal rate.

Although failure of thiouracil to reduce thyrotoxicity is seldom reported in the literature, we have had 3 patients with hyperthyroidism in whom thiouracil was ineffective. It is well known, however, that if iodine has been given before thiouracil is started, the beneficial effect of the latter drug will be reduced markedly.

Remissions. The number of patients whom we have observed over a prolonged period of time for determination of the possibility of a permanent cure or remission has been relatively small, namely only 26 cases. We have learned, as have others working in this field, that treatment for less than 6 months is not apt to produce a remission with any degree of permanency. With one or two exceptions, all the patients in this series of 26 had taken the drug for 6 months or longer. Ten of them had recurrence within 1 to 7 months. It is somewhat difficult to determine exactly when a recurrence takes place, largely because the symptoms develop so insidiously that the patient is not entirely aware of the exact date of recurrence of symptoms. Nine of the 26 patients have had no recurrence of symptoms for 8 to 17 months (average 12.1 months) fol-

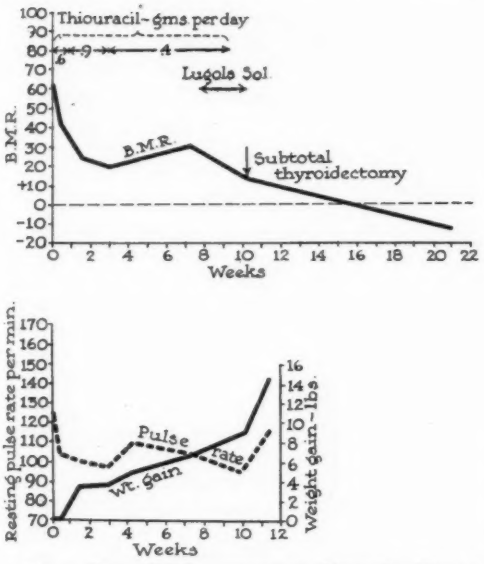

Fig. 3. Unusually slow response to thiouracil. After 73 days of therapy, the basal metabolic rate had receded only 45 points.

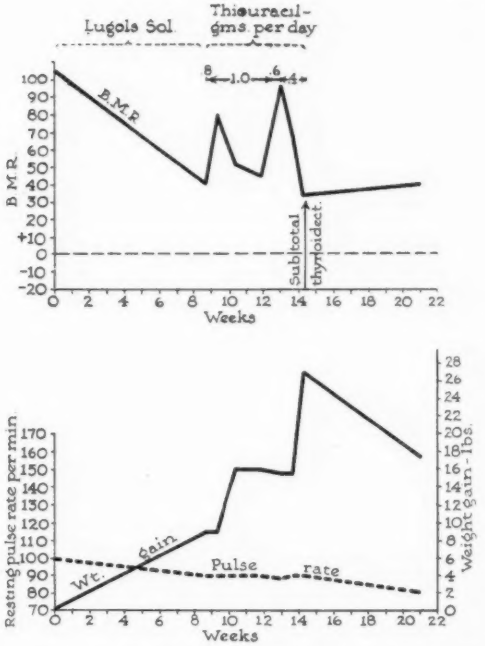

Fig. 4. Deleterious effect of preliminary course of iodine on thiouracil response. Previous to 6 weeks' treatment with thiouracil the patient had received Lugol's solution for 8¼ weeks. The 6 weeks period of treatment with thiouracil resulted in no reduction in basal metabolic rate although there was considerable weight gain and a slight decrease in severity of symptoms.

lowing cessation of thiouracil therapy. Seven of the 26 patients have had no recurrence of symptoms, but observation has been for a much shorter time, namely only 1 to 5 months following cessation of therapy. In general, we have found that patients with mild toxicity and those with relatively small glands are more apt to have a permanent remission than are other types of patients.

Determination of operability. In patients treated successfully with thiouracil it will rarely be necessary to make an appraisal of the patient's condition to determine operability or time for operation. However, there will be a small number of patients who will have reactions following thiouracil and a few who will not respond to the drug, thereby constituting an appreciable number of patients who must be treated by conventional methods, consisting mainly of iodine and operation. It took us three or four decades to learn how to determine operability and optimum time for operation in thyrotoxicosis. The authors wish to make a plea that the profession not abandon all this information which required years for accumulation. All of us have certain prerequisites to determine operability. Unfortunately, not many have taken the time or trouble to convert these prerequisites into terms that can be transmitted to others. From a teaching standpoint, we have learned that to transmit information of this type to students, it must be converted to mathematical status or its equivalent. We have utilized the pre-

TABLE V.—PREREQUISITES FOR BILATERAL THYROIDECTOMY IN TOXIC GOITER

1. Gain in weight and strength.
2. Resting pulse below 110.
3. Basal metabolic rate below 50.
4. Response to iodine or thiouracil.
5. No untreated complications.

During operation:
- If pulse rate goes to 135 not explainable on basis of anesthetic, consider possibility of removing only one lobe.
- If pulse rate goes above 145, indications are to stop the operation or remove only one lobe.

requisites in determination of safety for bilateral thyroidectomy in toxic goiter (Table V).

The surgeon has the opportunity to save many lives by asserting good judgment in the operating room. For example, as suggested in Table V, if the pulse rate goes to 135–140 unrelated to anesthesia, it is obvious that the patient was more toxic than the surgeon anticipated; therefore he should consider the possibility of removing only one lobe. On the other hand, if the patient's pulse rate goes to 145 or higher during the operation without relation to the anesthesia, the surgeon should consider stopping the operation at once or at least removing only one lobe. On many occasions the authors have returned patients to the ward when they arrived at the operating room with a fast pulse which did not settle down under anesthesia. If the pulse rate does not come down to 130 or thereabouts under anesthesia, the incision should be delayed; it may be wise to cancel the operation and wait several days for a more opportune time. This decision is particularly indicated if an excess amount of oxygen seems to be required during the anesthetic, and if there is difficulty in eliminating cyanosis.

SUMMARY

Thiouracil has been of great assistance in the treatment of hyperthyroidism. It will reduce the basal metabolic rate to normal in at least 95 per cent of patients with hyperthyroidism except that reactions may prevent continuation of the drug (in 9 per cent of our series). A survey of the literature reveals an incidence in reaction of 13.8 per cent. Agranulocytosis occurred in 0.78 per cent of patients (1,543 cases studied from the literature, with a mortality rate of 0.45 per cent). Besides agranulocytosis, reactions consisted of leucopenia, nausea and vomiting, dermatitis, pruritis, fever, swelling of the salivary gland, arthralgia and other minor complaints. In our series of 79 patients, reactions were slightly greater in number but of less severity than noted in the literature; we had no deaths attributable to thiouracil.

The greatest advantage of thiouracil over iodine is in the group of patients who are so toxic that bilateral thyroidectomy is unsafe under iodine therapy. The drug is particularly useful in patients with cardiac decompensation secondary to hyperthyroidism. In our experience about one-half of the patients treated will have remission of prolonged or permanent type but these patients must be chosen. Patients with mild toxicity and small glands are more apt to have permanent remissions than are other types. Patients with toxic diffuse goiter respond slightly better than do those with toxic nodular goiter.

The most serious disadvantage is the toxicity and, particularly, the mortality rate. The slow action is uneconomical; many surgeons and internists feel that treatment of patients with mild hyperthyroidism with iodine and thyroidectomy may be superior to the use of thiouracil, particularly since the mortality rate of operation is so low in that group.

Since there are numerous drugs which produce cessation of hormone formation, it is likely that a better drug will be found which will not be toxic. A new drug, propylthiouracil, appears to be much superior to thiouracil.

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OBSERVATIONS ON THE USE OF G-11 IN THE SURGICAL SCRUB

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THE following studies were undertaken in the attempt to confirm the observations of Traub and others (3, 4) who have reported the remarkable effect of the compound G-11[1] (2-2′-dihydroxy-3, 5, 6-3′, 5′, 6′-hexachloro-diphenyl-methane) in reducing the resident flora of the skin. In general we have been able to substantiate these results; the data presented below indicate certain modifications in the methods of using and evaluating the material which may be employed to advantage.

Traub found that persons using, for all skin washing purposes, a soap containing 2 per cent G-11 showed very low numbers of skin organisms when tested by the Price technique (2). He states (4) that if the material is to be used in a surgical scrub it must also be employed exclusively whenever soap is used on the skin; application only at the time of the actual scrub would be ineffective, since a preliminary period of contact is required for the action of the disinfectant to appear. Such a requirement presents some inconvenience, and more supervisory difficulty; the effectiveness of the agent has therefore been tested when its use was restricted to operating-room procedure.

According to Traub there is no evidence for the carry-over of disinfectant into the medium to account for the low numbers of organisms seen in the tests. Since his evidence for this is only indirect, we have examined the possibility in greater detail. Moreover, since the basis for the activity of G-11 must be primarily chemical, the effect of eliminating the scrubbing brush from the surgical wash was investigated.

Method of determining numbers of skin organisms. The technique was essentially that of Price as modified by Pohle and Stuart. The individual to be tested wet his hands to a point 1 inch above the wrist joint in 1 liter of sterile distilled water in a sterile basin. Ivory soap was applied to the wet skin area for 25 seconds, after which the subject massaged his hands thoroughly for 75 seconds. The hands were then rinsed in the basin for 25 seconds. Poured plates containing 0.1 and 1.0 milliliter of the thoroughly stirred basin water were prepared. Counts were made after 48 hours at 37 degrees C. The serial basin portion of the Price method was not used since the first basin, which gives the highest counts analogous to the dose of micro-organisms released in the event of tearing a glove, was our main interest. The skin counts reported here are expressed as the number of organisms per liter of wash water, or per basin.

Susceptibility of normal skin organisms to G-11. The plating medium in this experiment consisted of bacto-tryptose 1.0 per cent, bacto-beef extract 0.5 per cent, sodium chloride 0.5 per cent, and agar 1.5 per cent. A 1 per cent alcoholic solution of the monopotassium salt of G-11 was diluted serially in broth of the same composition as above. Organisms were tested both in broth and in agar. The stated concentrations of G-11 represent final concentrations in the medium. The strains employed were obtained from skin tests as described on two individuals who had gone through a thorough wash with plain green soap solution, and had worn sterile gloves for 45 minutes. They had not been in contact with G-11. Ten colonies were isolated from each; all 20 strains were staphylococci, either lemon yellow or nonpigmented. No gram negative forms were found. In testing G-11 in broth, 5 milliliter amounts containing 10 fold dilutions of G-11 were inoculated with 0.1 milliliter of a barely turbid suspension of the test organisms made from a 24 hour slant. Agar plates containing 10 fold dilutions of G-11 were inoculated on the surface with a loopful of the same suspen-

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[1]William S. Gump, U. S. Patent 2,250,480.

TABLE I.—INHIBITORY EFFECT OF WASHINGS FROM G-11 TREATED SKIN ON NORMAL SKIN ORGANISMS. SURFACE INOCULUM METHOD

		Subject A		Subject B		Subject C	
	Size of basin sample added to agar (ml.)	0.1	1.0	0.1	1.0	0.1	1.0
Medium	Test strain						
Tryptose-extract	1	±	—	±	—	+	—
	2	±	—	++	—	++	—
	3	+	—	++	—	++	—
	4	±	—	++	—	++	—
Infusion	1	+++	—	+	+	+++	—
	2	+++	—	+++	+	+++	—
	3	+++	—	+++	±	+++	+++
	4	+++	—	+++	+	+	—
Tryptose-extract 1% serum	1	All +++					
	2						
	3						
	4						

± indicates a barely perceptible film of growth.
+++ indicates growth equal to that on control plate.

sions, each spread over an area of about 1 square centimeter. Readings were made after 48 hours at 37 degrees C.

Three strains tested in broth were completely inhibited at a dilution of 10^{-6}, with partial inhibition at 10^{-7}. Twenty strains were tested on agar; at a 10^{-6} dilution 2 strains showed only partial inhibition, 3 showed almost complete inhibition, and the remaining 15 failed completely to grow. At 10^{-7} all 20 strains grew as well as on the control plates. Three gram negative organisms (coliforms) tested in the same manner, grew in concentrations of G-11 10 to 100 times greater. Parallel tests on zephiran chloride showed similar bacteriostatic levels, including the greater resistance of gram negative bacilli.

Bacteriostatic effect of wash waters obtained from individuals in contact with G-11. In view of this demonstration of marked bacteriostasis in low concentrations of G-11, the wash waters obtained from skin tests on persons in contact with G-11 were tested directly for their bacteriostatic effect when incorporated in agar plates in 0.1 and 1.0 milliliter amounts. Three persons who had been subjected to the standard G-11 surgical wash (see below) once daily for 5 days, followed by a 2 day lapse, were again given the standard G-11 wash and required to wear dry sterile gloves for 45 minutes. They were then tested, and the wash water added to agar plates in 0.1 and 1.0 milliliter amounts. Four of the strains from normal skin were tested by inoculation onto the surface of these plates. The results are given in Table I, showing that with the medium described in the previous section, marked inhibition was present in the plates containing the 1.0 milliliter samples against all 4 strains, with partial inhibition in the 0.1 milliliter samples. Taking into account the 10 fold dilution of wash water in agar with the 1.0 milliliter sample, from 1 to 10 milligrams of G-11 may be carried over into the basin from the skin under these conditions. On a few occasions there has been evidence of slight inhibition from samples obtained 24 hours after the last G-11 application, but this was less striking than that seen in samples taken 45 minutes after contact. In no case was a G-11 soap used in the procedure for obtaining skin counts.

In the attempt to neutralize this inhibitory effect in the medium, infusion agar was tested, since it had been employed by Traub with no indication of bacteriostasis. It is evident in Table I that some neutralization has occurred since the 0.1 milliliter samples, with a few exceptions, showed no inhibition. However, the 1.0 milliliter samples were still markedly inhibitory. The addition of sterile sheep serum in a concentration of 1 per cent to the tryptose-extract agar completely obliterated the bacteriostatic effect of the traces of G-11 carried over from the skin, Table I. In explanation of this effect it was found that the bacteriostatic potency of G-11 was depressed about 100 fold by the addition of 1 per cent serum to the agar or broth used for testing.

The method of testing for bacteriostasis given, in which relatively large numbers of organisms are applied to a small agar surface, is not as sensitive as are poured plate tests in which isolated organisms are exposed to the material. Therefore, poured plates containing known numbers of normal skin bacteria in the presence of measured amounts of wash water were prepared in order to approach more closely the conditions under which the skin counts are obtained. The results are given in

Table II; the inhibitory effect of 1.0 milliliter of wash water (Specimen A in Table I) was again demonstrated in all media except those containing 1 per cent serum. The substitution of Witte peptone for tryptose resulted in only slight improvement. It is difficult to reconcile these findings with those of Traub, who disclaims any such effect. He does not state the interval between the last application of G-11 and the collection of the sample; in his studies, this interval would presumably be variable. It is possible that his infusion medium happened to contain more inhibitory substances than did ours. As a result of these observations, all counts referred to hereafter were made in tryptose-extract agar containing 1 per cent serum, unless otherwise specified.

TABLE II.—INHIBITORY EFFECT OF WASHINGS FROM G-11 TREATED SKIN ON NORMAL SKIN ORGANISMS. POURED PLATE METHOD

	Test strain							
	1	2	3	4	11	12	13	14
Medium								
Tryptose-extract agar+1 ml. wash water A. No serum.	10	2	0	0	0	0	89	0
Infusion agar + 1 ml. wash water A. No serum.	40	137	104	42	112	48	82	24
Witte peptone-extract agar+1 ml. wash water A. No serum.	65	31	69	7	11	6	65	57
Tryptose-extract agar+1 ml. wash water D. No serum.	564	236	204	528	456	250	79	208
Tryptose-extract agar+1% serum+1 ml. wash water A.	534	252	184	552	474	312	89	214
Tryptose-extract agar+1% serum. No wash water.	468	260	206	564	450	223	80	276

Plates represented in each vertical row received the same number of organisms. As is evident in the last horizontal (control) row, the numbers of organisms in the inoculum varied from one strain to another.

Wash water A from subject A (Table I) washed with G-11 45 minutes before sample was taken. Culture on 1 ml. of wash water alone+1% serum gave 1 colony.

Wash water D from an individual treated with control soap without G-11. Remainder of treatment was the same including the zephiran rinse. These washings were autoclaved before use. Culture was sterile.

Surgical wash with G-11. A liquid soap containing G-11 was used since a more uniform application is possible, in contrast to a bar soap with which an undeterminable amount is applied to the skin. A 1 per cent preparation was finally adopted, made as follows: 10 grams of the monopotassium or monosodium salt of G-11 were dissolved in 50 milliliters of hot 95 per cent ethyl alcohol. The alcoholic solution was added with thorough mixing to 1 liter of soap solution prepared by dissolving 200 grams of clear potash soap in 800 milliliters of hot distilled water. Both solutions were cooled before mixing. The final product contained 5 per cent alcohol and all control soaps were also made up to 5 per cent alcohol for comparison. The standard wash procedure was as follows:

1. The hands and arms were wet in tap water and a large palmful of G-11 soap solution applied to each hand and arm. Persons with small hands used 2 palmfuls. Over a period of 1 minute the soap was lathered into the hands and arms.

2. This was allowed to remain for 2 more minutes during which waiting period the nails were cleaned.

3. After a tap water rinse, 1 and 2 were repeated, with the omission of the nail cleaning. Thus the skin was in contact with the solution over a 6 minute period.

4. After another tap water rinse the hands and arms were immersed for approximately 5 seconds each in an *aqueous* solution of zephiran chloride 1:1000 and dried on a sterile towel. The disinfectant rinse contributes nothing to the effect beyond destroying hypothetical organisms in the tap water left on the hands. If a fresh sterile water rinse is available for each individual, the zephiran rinse may be omitted.

In testing the effectiveness of this procedure under various conditions, the test subjects, after washing, powdered their hands with sterile talc and wore dry sterile gloves for 45 minutes before determining the skin population. Questions relating to practical operating-room routine were investigated. Direct comparison with a conventional 10 minute surgical scrub with a brush, followed by an alcoholic zephiran chloride 1:500 rinse was carried out. The effectiveness of the *first* G-11 application was tested. The not uncommon practice of changing gloves between operations with only a limited skin cleansing was also considered in relation to the use of G-11. The effect of its interrupted, or nondaily use was examined, and its effectiveness in alcohol, rather than in soap solution, was tested.

Five subjects, 3 men and 2 women, were tested through 3 consecutive mornings of

TABLE III.—COMPARISON OF SURGICAL SCRUB AND G-11 WASH

Day and procedure	Subject	First 45 minutes	Second 45 minutes	Third 45 minutes
First day. 10 minute scrub with Ivory soap, 1:500 alc. zephiran rinse. Same rinse preceding each glove change.	A	215	60	235
	B	720	890	1510
	C	1330	870	830
	D	73	46	25
	E	106	37	122
	Average	489	380	544
Second day. 6 minute standard G-11 wash. 1:1000 aqueous zephiran rinse. Same rinse preceding each glove change.	A	45	219	129
	B	63	63	120
	C	211	254	370
	D	35	24	44
	E	42	68	65
	Average	79	126	146
Third day. Same as second day.	A	2	90	50
	B	28	123	85
	C	6	12	23
	D	2	4	5
	E	2	less than 1*	20
	Average	8	46	36

*Less than 1 (less than 1000 per liter) indicates that the plate containing 1.0 ml. of wash water was sterile.
Each skin count obtained after 45 minutes in fresh sterile gloves.
Multiply figures by 1000 to obtain counts per liter of wash water.

simulated operating-room conditions. None had been in contact with G-11 previous to the experiment. The results appear in Table III. On the first day they scrubbed for 10 minutes with Ivory soap, cleaning the nails during the scrub. They then rinsed in tap water and in a 1:500 zephiran chloride solution in 70 per cent alcohol. The hands were dried on a sterile towel, and dry sterile gloves worn for 45 minutes during which the usual laboratory work was performed. The skin organisms were then estimated, the residual Ivory soap resulting from this determination rinsed off in tap water, the alcoholic zephiran rinse repeated, the hands dried on a sterile towel and gloves again worn for 45 minutes. This was repeated, giving a total of three 45 minute periods in gloves. On the second day, the standard G-11 wash was introduced; no brush was used. Again 3 glove changes at 45 minute intervals were made, and the aqueous 1:1000 zephiran rinse was used throughout. This procedure was repeated on the third day. It will be noted that only two 6 minute applications of G-11 soap were made; the material was not used at any other time.

TABLE IV.—SKIN COUNTS AFTER 5 SINGLE DAILY G-11 APPLICATIONS

Subject	Count
F	2
G	less than 1
H	2
I	5
J	2
Average	2.4

Three glove changes on fifth day with brief G-11 wash preceding each. Counts after third 45 minute period in gloves.
Multiply figures by 1000 to obtain counts per liter of wash water.

Several points of practical interest are seen in Table III. The rise in the skin population following a surgical scrub with glove changes is apparent, and is in agreement with the findings of Price. Moreover, the first application of G-11 without previous contact results in counts lower than those obtained with a surgical scrub. An individual could be introduced into a surgical group after only one 6 minute contact with G-11, although an additional contact on the preceding day would be preferable. The progressively increasing effectiveness of the agent is seen in Table III from the counts obtained on the second day of its use.

The data presented in Table III do not represent the maximum effect obtainable, probably because the 3 skin counts performed on each person each day, with the attendant prolonged Ivory soap lathering, extract G-11 from the skin. It has been found that alcohol rinses have the same effect and are to be avoided. To demonstrate a greater effect of the material which would obtain under normal conditions of use, 5 other persons, 3 men and 2 women, were given the standard G-11 wash daily for 4 days. No skin testing was done, nor was any other G-11 used. On the fifth day they changed gloves at 45 minute intervals as before, but, instead of being tested between each change, they washed their hands briefly (15 seconds) with G-11 soap, rinsed with tap water, and with aqueous zephiran. The counts appearing in Table IV were obtained at the end of the third 45 minute period and were consistently low throughout. These superior results are attributable to the

TABLE V.—EFFECT OF A 2 DAY LAPSE OF G-11 APPLICATION

Subject	Count
A	9
B	28
C	1
Average	12.7

Multiply figures by 1000 to obtain counts per liter of wash water.

maintenance of a higher level of the agent in the skin, and show that a brief wash with G-11 between glove changes will prevent the rise in bacterial numbers which occurs with ordinary procedures.

Effect of interruption of daily G-11 applications. Three persons, after going through the standard G-11 wash for 5 days were not treated for 2 days. On the third day thereafter they again carried out a standard wash, wore gloves for 45 minutes, and were tested. The results appear in Table V, and indicate that there is a persistence of the effect over this interval. It seems unnecessary to subject the surgical team to daily contact with the agent in order to maintain the effect, unless a lapse of more than 2 days takes place.

Effectiveness of G-11 in alcoholic solution. It was found that 33 per cent ethyl alcohol by volume was required to hold 1 per cent of the monopotassium salt of G-11 in solution at room temperature. The effectiveness of this 1 per cent G-11 in dilute alcohol in contrast to a solution of the material in 20 per cent soap was tested as follows: 5 subjects who had not been in contact with G-11 for over a month washed their hands briefly (about 15 seconds) in Ivory soap and cleaned their nails. They then rinsed in tap water and dried on a non-sterile clean towel. After immersing each hand for about 5 seconds in the alcoholic G-11 solution they allowed this to remain for 2 minutes after which they repeated the 5 second G-11 immersion, again allowing it to remain on the hands for 2 minutes. This time interval was employed since the skin dried almost completely in 2 minutes after the first immersion. Following a tap water rinse, the hands were immersed for about 5 seconds each in aqueous zephiran chloride 1:1000 and dried on a sterile towel. Gloves were worn for 45 minutes followed by the usual estimation of skin organisms. The results obtained on the second day of this treatment, including 3 control persons treated in the same manner except for the substitution of 33 per cent alcohol without G-11, are shown in Table VI. It may be seen that the alcoholic G-11 is as effective as a soap solution of the agent, however, the possibility was pursued no further because of the marked preference of the subjects for the soap solution, which proved to be considerably less irritating. It appears that more G-11 is released into the test basin in this procedure than was found in the studies on soap solutions. Five per cent serum was required to eliminate the bacteriostatic effect of these washings in contrast to the 1 per cent serum needed for the soap solution of G-11.

TABLE VI.—EFFECT OF ALCOHOLIC SOLUTION OF G-11

Second day of treatment with G-11 in 33% alcohol without soap. Counts made after 45 minutes in gloves.

Subject	Count
A	9
B	2
C	1
D	3
E	1
Average	3.2

Control counts of individuals using same procedure but omitting G-11 from the alcohol. Second day of treatment. Counts made after 45 minutes in gloves.

Subject	Count
F	135
G	4400
H	920
Average	1818

Multiply figures by 1000 to obtain counts per liter of wash water.

DISCUSSION

The compound G-11 incorporated in soap appears to be a valuable agent in the cleansing of skin. The available evidence suggests that it is taken up by skin and retained for considerable intervals exerting a constant bacteriostatic (if not bactericidal) effect on the resident flora. It is equally effective in dilute alcohol solution, but this has been found to be more irritating than the soap preparations. Under certain conditions bacteriostatic amounts of G-11 are extracted from the skin and carried over into the medium in the process of enumerating the skin bacteria, a fact which must be recognized as a source of error in evaluating effectiveness. With proper attention to details of concentration and length of exposure of the skin to this agent, the use of both the scrubbing brush and the somewhat irritating alco-

hol rinses may be eliminated from preparation of the surgeon's hands and arms. Its exclusive use whenever soap is employed is unnecessary for persons going through a single surgical wash, as outlined above, on each of 5 days a week. Lapses of longer than 2 days reduce the effectiveness of the material. No irritation or sensitivity has been encountered in our studies on G-11 with the exception of one scrub nurse who developed a measles-like eruption about 6 hours after her first application. This disappeared on subsequent applications. It would not be surprising if occasional instances of true sensitization were to appear.

Another obvious use of G-11 is in the preparation of the patient's skin in elective surgery in which a few days are available to attain the full effect. It should be pointed out that G-11 is not a substitute for more potent materials such as iodine which, though limited to the superficial skin organisms, exert a prompter action. For example, the contamination of the skin by pus would have to be dealt with in the usual way. One might anticipate that G-11 would be ineffective in open wounds in view of the inhibitory effect of serum.

SUMMARY

The incorporation of G-11 (2-2′-dihydroxy-3,5,6-3′,5′,6′-hexachloro-diphenyl-methane) in soap used for the preparation of the surgeon's skin reduces the numbers of skin organisms considerably below those found after conventional scrub procedures. Broadly speaking, bacterial counts of the washings of untreated hands range in the millions of organisms per liter. Conventional surgical scrubs followed by germicidal rinses reduce the number about tenfold, and the G-11 wash accomplishes a reduction of about a thousandfold from normal skin counts. In addition, the time consumed is shorter, and the scrubbing brush and strong germicidal rinses are unnecessary.

Individuals receiving the 6 minute application described, once each day, 5 days per week, would require no further daily contact with G-11 to maintain its effect. When changing gloves between operations, a brief wash with G-11 soap is sufficient to keep the skin counts at a low level. Prolonged lathering with plain soaps, and the use of alcohol rinses decrease the effect, presumably by extracting G-11 from the skin.

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PLASMA FRACTIONS—"FIBRIN FOAM," THROMBIN, AND "FRACTION NO. 1"—IN GENERAL SURGERY

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An active preparation of beef thrombin was announced by Mellanby in 1933. Seegers and McGinty later reported a preparation of greater activity. Parfentjev's monograph on the fractionation of rabbit plasma provided the basis for the study of the globulin-containing fraction with thrombic activity (18). Several clinical applications of animal thrombin were reported by Tidrick. Additional reports on its use in diseases with prolonged bleeding time (hemophilia, symptomatic thrombocytopenic purpura, hypoprothrombinemia, and hereditary thrombasthenia) were made by Lozner and his associates. The antigenicity of thrombin was studied by Light (11) who also, with others (12, 16), reported the use of thrombin applied on special gelatine sponges instead of fibrin foam.

Cohn and his co-workers, in fractionating pooled human plasma, produced "fraction No. 1," thrombin, and "fibrin foam."

Foam is a sponge-like, brittle solid which, soaked in thrombin, becomes gelatinous and, applied topically, produces rapid clotting. For more detail of the physical and chemical properties the reader is referred to the original reports (3, 7, 8).

Bailey and Ingraham (2, 9) studied the hemostatic properties of the foam thrombin combination. In the experimental animal, bleeding from wounds in the liver, peritoneal cavity, kidney, and lungs was controlled. It was shown that the presence of foam did not impair the efficiency of the sulfa drugs or penicillin. Use of the foam thrombin combination in man first was reported by Ingraham (10) and later by Woodhall, both of whom used it in neurosurgical operations. Anderson and Kentros reported a successful application at dental extraction in the case of a hemophiliac patient.

Cohn's "fraction No. 1," derived from plasma, consists of light amorphous particles which are approximately 80 per cent fibrinogen. Cronkite and others are credited with the first application of fibrinogen and thrombin as an adhesive for skin grafts. Dees reported their use at pyelolithotomy to form a coagulum in the pelvis which would trap stones.

We have used plasma fractions, obtained through the courtesy of Drs. Franc D. Ingraham and John T. Edsall, 250 times in 210 patients. The fractions used were thrombin, fibrin foam, and fraction No. 1. The purpose of the study was the development of applications for these substances in general surgery.

THROMBIN

Thrombin alone, applied on a sponge, was used in 2 cases. The results were unsatisfactory.

FRACTION NO. 1 AND THROMBIN

Fraction No. 1 and thrombin were used in 12 cases: to remove gravel from a renal pelvis in 1 case, with only partial success; as an adhesive for the skin flaps in 9 mastectomies; as an adhesive under split thickness graft in 1 case; around a split thickness skin graft in the making of an artificial vagina in 1 case. Results were good except in 3 cases in which more than the usual amount of serum accumulated, lifting parts of the skin from the bed. In 1 of the latter cases infection developed with extensive loss of graft. The fluid accumulation may have been fortuitous, or it may have been from overproduction of secretion. We suspect, however, that it was from mechanical interference with drainage. Therefore, we now are making it a practice to leave channels for

The products of plasma fractionation employed in this work were developed from blood which was collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston Massachusetts, under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

TABLE I.—HEMOSTASIS OF INCISIONS INTO SOLID ORGANS

	No. Cases
Thyroid (cut surface)	12
Cervix (biopsy, conizaetion, avulsion of polyp)	10
Uterine sinuses (cesarean section)	3
Uterine wall (myomectomy)	2
Liver (laceration)	2
Kidney (nephrostomy)	2
Pancreas (resections)	3
Suprarenal gland (biopsy)	1
Breast (biopsy)	8
Total	43

drainage and inserting small rubber tissue drains.

FOAM AND THROMBIN

Fibrin foam soaked in thrombin was used 236 times in 196 patients for one or more of three purposes: first, as a hemostatic; second, as a filler of cavities; and third, as a dressing.

1. *Use as a hemostatic.* While the bleeding is controlled by pressure, a block of foam, cut to size by razor blade or scalpel, was soaked in fresh saline solution of thrombin. The resultant jelly-like mass then was held against the bleeding area by gentle pressure with a sponge or, preferably, the finger itself. Sometimes it was advisable to remove by suction excess thrombin which might interfere with adherence of foam.

Usually clotting was instantaneous. To some degree clotting time depends upon the strength of the thrombin solution. Occasionally one portion of the bleeding area continued to bleed. We interpreted this as meaning that the amount of thrombin in the first application was insufficient or that the application to the bleeding area was uneven. Invariably bleeding was controlled by a second or third application. We found that the release of pressure should be gentle to avoid disturbing the clot. Before foam was used it often was advisable to control the oozing by simple pressure until manipulations in the immediate neighborhood were finished. Sometimes it was advantageous to prepare in advance a flap of peritoneum or other tissue to suture over the foam pad. Interestingly, this work with foam increased our respect for simple pressure as a hemostatic. Oozing areas ordinarily were controlled by pressure while foam was being prepared. Sometimes bleeding which we would not have expected to control without suture had stopped by the time foam was ready. However when foam was used in addition we felt more secure against recurrence. Because of the possibility of generalized intravascular thrombosis, never under any circumstances should thrombin be injected intravenously. To prevent accidental aspiration into open veins on a bleeding surface one should apply pressure enough to close the veins from the instant when the pad is applied until clotting is complete.

The most commonly useful application was at thyroidectomy. Only the larger spurting vessels were clamped, with 8 to 12 instead of 20 to 40 clamps per lobe. These clamps were tied. No second round of clamps was applied. The gland remnant was not sutured. Sheets of foam on the cut surface completed the hemostasis. The advantage is not just reduction of sutures and clamps. It is avoidance of trauma to the thyroid remnant. One may intend to leave a fifth or sixth of the gland. But if the sixth is full of compressing ties and sutures it may be, physiologically, a tenth. Also, the usual final suture of the gland remnant endangers the recurrent nerve behind the gland and necessity for this suture is eliminated by the use of foam.

Pancreatectomy demonstrated another useful application. In 1 case a considerable amount of pancreatic parenchyma at the junction of body and head was resected. Both pancreatic ducts were cut. One was ligated; the other anastomosed after resection of 3 centimeters. Foam was packed into the cavity and around the anastomosis. The cut surfaces were sutured together and the suture line covered by a foam dressing. The patient died on the 9th postoperative day from pancreatitis and bronchopneumonia. Postmortem examination showed leakage at the anastomosis but no bleeding. A cardiac patient whose pancreatic resection had necessitated anastomosis of the duct died from cardiac decompensation on the 5th postoperative day. Postmortem examination showed no infection or pancreatitis. The anastomosis was tight and there was no evidence of hemorrhage.

Foam not only has controlled bleeding from incisions into pancreas, liver, and kidney, but

by replacing deep sutures it has avoided the bleeding which such sutures themselves cause and the danger to ducts which they involve. At every application in this group the foam was completely successful in hemostasis, usually at the first application but sometimes only at the second, or rarely the third.

Foam thrombin purposely was used 17 times in the skin or in the immediately subcutaneous tissues to allow naked eye observation of healing. The group included 10 applications at herniorrhaphy. No gross difference was observed in those parts of the wounds where the foam was implanted.

Throughout this group of applications foam invariably succeeded in controlling bleeding. Foam thrombin was particularly beneficial when applied to tissues distorted by pathology which lay near vulnerable structures such as the hepatic duct, the ureter, the hypoglossal, spinal accessory or phrenic nerves. Here foam substituted for blind clamping and deep suture. Commonest application in this group was to the subvesical veins at hysterectomy and in vaginal operations. The areolar tissue of the neck, erectile tissue of the labia, retroperitoneal spaces, mesentery, and intestine proved practical sites for application. Several times foam was used for minor oozing around the cystic artery stump which otherwise would have been left uncontrolled for fear of injuring hepatic ducts by clamping. Profuse bleeding from one severed aberrant cystic artery or major branch thereof was stopped immediately by foam. Following proctoscopic resection, bleeding from the base of a good sized sigmoidal polyp was controlled by foam held in place by suture.

We did not use foam for control of direct hemorrhage from large vessels in the human. The largest artery that we tried to control, and it was controlled immediately and satisfactorily, was the rather small cystic artery referred to in a patient with normal blood pressure. However in 8 operations upon dogs, major arteries up to 4 millimeters in diameter were opened or transected. At normal blood pressure, arteries of 2 millimeters and sometimes those of 3 millimeters were controlled by foam and digital pressure. Some clots blew off when hypertension was induced. After the blood pressure had returned to normal, new applications of foam held. Two arteries of 4 millimeters could not be controlled by foam until the blood pressure had fallen to dangerous levels.

TABLE II.—HEMOSTASIS ON SOFT SURFACES OR IN AREOLAR SPACES

	No. Cases
Skin and subcutaneous tissues	17
Base of bladder or broad ligaments	
Vaginal operations for prolapse	14
Abdominal hysterectomy	10
Gall bladder	
Pedicle	5
Bed	15
Stomach, intestine, mesentery	
Resections, incisions, abscess walls	19
Kidney pedicle	1
Retroperitoneum (sympathectomy)	8
Deep tissues of neck	5
Axilla, inguinal region (gland dissection)	8
Vulva (vulvectomy)	2
Varices (stripping)	5
Hemorrhoids (hemorrhoidectomy)	8
Total	117

We do not propose the use of foam for openings in major vessels. In arteries there is the risk of delayed hemorrhage from a high head of pressure acting over a broad area. In veins there is the risk of indrawn thrombin. However, suddenly faced with a laceration of the vena cava, one of our colleagues held a pad of foam on the opening by suturing peritoneum over it. The patient ultimately came to postmortem examination, which showed neither hemorrhage at the site of operation nor distant thrombosis.

It is reiterated that foam is not recommended for the large vessel, whether artery or vein.

2. Use as a filler of cavities. In 31 cases foam thrombin was used as a hemostatic filler which later was replaced spontaneously by reparative tissues. Usually only a small amount was needed. However, we have used up to approximately 25 cubic centimeters without bad

TABLE III.—FOAM THROMBIN AS FILLER OF CAVITIES

	No. Cases
Coccygectomy	2
Excision Bartholin's cyst	7
Excision wen	15
Excision pilonidal sinus	2
Excision ganglion	4
Excision lipoma	1
Total	31

effect. In our experience, the most satisfactory application of foam, after thyroidectomy, was in the removal of a Bartholin's cyst. Often in the past the small artery at the upper end of the cyst escaped our clamps, retreated into the spongy perivaginal tissues, and bled. Wounds of operations for pilonidal sinus, wen, and ganglion, that is, cavities which could be watched from the surface, healed well with foam fillings. In addition to the cases listed in Table III, considerable amounts of foam were used in deeper cavities in other cases listed in Tables I and II (e.g., presacral neurectomy, breast biopsy, some of the gastrointestinal resections) with the secondary purpose of space-filling. None of these cases showed complications attributable to foam.

3. Use as a dressing. Following an accidental observation that better epithelium seemed to grow more quickly under foam, foam thrombin dressings were applied to 2 skin defects and 2 small mucosal defects (epulis, rectal polyp) and the results were satisfactory in each.

After preliminary trial in the dog, foam also was used 5 times as an internal dressing wrapped around an intestinal anastomosis and as mentioned previously foam dressing has been used around pancreatic duct anastomosis. It was used once over an incision into the renal pelvis, with inconclusive result. There seems to be some indication for its use in anastomosis but our experience has been too limited to be conclusive. In 2 cases of femoral embolectomy, foam worked well as an outer coat around the artery. However, because of the normal risk of thrombosis in arteriorrhaphy, our judgment in applying foam in these instances was questionable.

Foam proved an excellent dressing after anal operations. The anuscope could be reinserted after operation without fear of hemorrhage when it was followed by a foam thrombin plug in the anal canal. Foam from containers which had been opened for other operations was used for anal cases.

COMPLICATIONS

The absolute contraindication to the injection of thrombin intravenously and the danger of accidental aspiration into an opened vein on a surface or in a cavity, which we have tried to prevent by preliminary digital pressure, have been mentioned. Two of our 210 patients had femoral thrombosis. This incidence is high but the group is too small to form definite conclusions. It should be recorded also, that the group was picked from a larger series and contained most of those individuals of the total who were likely candidates for thrombosis. The increased accumulation of fluid under skin flaps or grafts when fraction No. 1 and thrombin were used was produced more by interference with drainage, we believed, than by increased secretion. The consequent advisability of leaving drainage channels has been mentioned.

No other complications were met. Foam was used freely in conjunction with topical sulfathiazole or penicillin. Foam was used in infected cavities when they were near enough to the surface so that they could be watched; no complications were noted in these cases.

SUMMARY AND CONCLUSIONS

A few experiences with fraction No. 1 and thrombin are recorded. In 236 applications, foam thrombin proved an efficient hemostatic agent for incisions into solid organs and at sites such as soft surfaces or areolar spaces where ordinary methods of hemostasis are difficult of application or unsatisfactory in result. It may substitute for blind clamping and deep suture with their consequent danger to adjacent vulnerable structures such as a hepatic duct, ureter, or nerve. It should not be used for large arteries or veins. Complications and dangers are discussed.

These blood fractions like their parent fraction, plasma, are neither an excuse for sloppiness in technique nor a substitute for judgment. But, like plasma, they promise to extend a little the present boundaries of technical operability.

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CLINICAL OBSERVATIONS ON FURACIN SOLUBLE DRESSING IN THE TREATMENT OF SURFACE INFECTIONS

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FOLLOWING the report by Snyder, Kiehn, and Christopherson that 5-nitro-2-furaldehyde semicarbazone (furacin) 0.2 per cent in a water soluble base (furacin soluble dressing) was effective in the treatment of infected battle wounds, a study of this preparation on a series of infected surface lesions encountered in the patients in a civilian hospital was begun. The material presented here is the clinical and bacteriological results obtained during the local treatment of 90 cases of superficial infections.

FURACIN

Furacin is a yellow, crystalline material having the structural formula O_2N- $-CH=NNHCONH_2$. It has been shown by Dodd and Stillman (2, 4) to be both bacteriostatic and bactericidal for a variety of gram-positive and gram-negative pathogenic bacteria, and Cramer and Dodd (1) have demonstrated that the activity is maintained in the presence of body fluids. In addition, oral administration of the compound has been found (2) to produce a therapeutic effect on experimental infections in mice with both gram-positive and gram-negative bacterial species. Tests (3) in both rabbits and humans have shown the material to be nonirritating upon local application and no toxic symptoms have been observed in animals on which large amounts have been applied for long periods of time. Meleney and Johnson (7) have recently stated that this compound is active against gram-negative bacteria and satisfies the requirements for use in the local treatment of infection.

The compound is fairly insoluble in water (1-4100). However it was used as a 0.2 per cent solution in a mixture of "carbowaxes" and propylene glycol in which it is soluble up to a concentration of 1.0 per cent. This base is water-soluble, nonirritating and nontoxic, liquefies at body temperature and can be removed easily without scrubbing by washing with water. Many investigators (5, 8, 9) have reported on the safety of the ingredients. Recently, Meleney and Johnson (7) have noted the advantages of this type of base for local use on the skin.

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PROCEDURE AND METHOD OF EVALUATION

In all cases the preparation was applied to the area to be treated so as completely to cover the area. On superficial infections furacin soluble dressing was spread on gauze handkerchiefs, and laid over the wounds and held in place with gauze bandage. Deep wounds and cavities were filled with the ointment, and a dry dressing used to cover the area. Sinus tracts were irrigated with the melted ointment. Many patients were treated by covering the area with furacin soluble dressing without bandaging.

Cultures were taken by swabbing the worst appearing area of the wound following the removal of the ointment, every other day, or at the time the dressings were changed if they were left in place for longer periods. Ninety-seven of the strains isolated were tested *in vitro* for susceptibility to the drug.

It was realized that the evaluation of a new agent of this type is a very difficult task. As a result, an attempt was made to control as many of the extraneous factors as possible, such as bed rest, systemic therapy, and surgical intervention.

Also, the same criteria for evaluation were used wherever possible throughout the study, and classification of results was done according to the method proposed by Meleney (6) for the evaluation of the effect of materials

following local application. He advises the division of results into four groups, (a) brilliant, (b) good, (c) questionable, and (d) with no effect. In order to prove any definite benefit from a material, Meleney (6) believes that without controls, the results must fall into the brilliant or good classes in most cases.

CLINICAL RESULTS

Following the classification given, it was found that of the 90 cases reported, 26 fall into the brilliant group, 44 into the good group, 13 into the questionable group, and 7 into the group showing no effect. Thus, 77 per cent of the cases fall into the first two groups which fact would definitely qualify the treatment as valuable by this classification. It must be realized that many of the lesions treated consisted of a superficial infection superimposed on a previously existing skin lesion, such as lupus vulgaris, herpes zoster, or erythema multiforme. No effect was noted on the original condition in these cases, but the superficial infection responded well and rapidly to the application of furacin soluble dressing. The number and types of lesions treated and the results are summarized in Table I.

In the treatment of diabetic gangrene, it has been realized that any local application, including furacin soluble dressing, has no effect on the infection and on the gangrenous process unless early, adequate surgical intervention is carried out. Unless adequate drainage is instituted early, furacin soluble dressing will not prevent a lymphatic or tendon sheath spread of the infection upward. In the 8 cases of diabetic gangrene reported, 6 cases showed good results. In each of these 6 cases, early, adequate surgery was instituted. In 2 cases, surgery was not carried out, but it was found that where furacin dressing came in contact with the infected areas that were draining well, there was a marked improvement. There was a marked decrease in the odor from all 8 patients treated with furacin soluble dressing.

Two patients with compound fractures were treated with furacin soluble dressing. This ointment stops any spread of infection, and prevents to a great extent the slough and the drainage seen following a large compounding of a fracture.

TABLE I.—LESIONS TREATED WITH FURACIN

Diagnosis	No. cases	Brilliant	Good results	Questionable	No effect
Diabetic gangrene	8	0	6	2	0
Compound fracture	2	1	0	1	0
Chronic osteomyelitis	3	0	0	1	2
Loss of skin—burns and avulsion	8	3	3	2	0
Various skin lesions with secondary infection	28	14	12	2	0
Abscess	6	1	3	1	1
Wounds	10	2	5	1	2
Ulcers	15	2	10	3	0
Epidermophytosis	6	3	2	0	1
Acne vulgaris	4	0	3	0	1
Total	90	26	44	13	7

Three patients with chronic hematogenous osteomyelitis have been treated by irrigation of sinuses with the melted ointment, and by local application. The results here have been very disappointing. In 1 patient there was some reduction in the amount of drainage, and some tendency to heal, but these results were entirely questionable.

Under the heading of loss of skin we have classified the patients who have been burned and patients who have had avulsion of large areas of skin. In each case, there has been a marked reduction in the number of organisms present on culture. There has been a very marked reduction in the discharge from the wound, and all wounds have healed and granulated well. In 6 cases in which skin grafting has been carried out, either by the split-thickness or pinch technique, the majority of the grafts have taken. In none of these cases was an attempt made to clean the recipient area of the furacin soluble dressing before the grafts were applied.

In 28 cases of infected lesions of the skin, such as lupus vulgaris, erythema multiforme, chronic eczema, and herpes zoster, the results could be classified as brilliant in 14, and as good in 12. In every case, the infection was superficial, and the ointment could reach the invading organism. Two cases, 1 of tuberculosis cutis and 1 of lymphogranuloma inguinale, showed only questionable results.

The treatment of deep-seated abscesses such as deep abscess of the buttock and ab-

scesses of the thighs following infusions, the ointment has been of no avail unless early, adequate surgery and drainage have been carried out. If drainage is adequate and the abscess cavity is packed with furacin soluble dressing, the walls appear healthy in 48 to 72 hours, and healing time is shortened by several days. At the same time, the odor and discharge from these wounds are markedly reduced.

Many infected wounds have been seen at this hospital, either following an operative procedure or following trauma, and it has been found that if these wounds are adequately drained surgically and the ointment is applied, there will be a marked reduction in the number of invading organisms, a reduction in the amount of drainage, and a great diminution in the odor from the infected area. One patient developed a fulminating wound infection in a right paramedian incision which followed an emergency small bowel resection. Twenty-three days after the development of this wound infection but while the wound was still open, the patient developed an obstruction. A left paramedian incision was made with no attempt being made to wall off the original infected wound. The second incision did not become infected, both wounds having been covered with furacin soluble dressing.

Fifteen ulcers of the leg due to vascular disturbances have been treated with furacin soluble dressing. In each case, the superficial infection has been controlled very well and very rapidly. No change has been noted in the primary lesion except those changes that would be compatible with an improvement in the infection. These ulcers granulate well, and there seems to be no retardation of epithelization. Several of these ulcers have been skin grafted over furacin soluble dressing with an excellent take of the grafts.

Six cases of acute athlete's foot have been treated with furacin soluble dressing. There is almost an immediate response of the secondary infection superimposed on the epidermophytosis, and the patients noticed much relief in 12 hours. In 3 cases, the patients have noticed a rapid healing of the original epidermophytosis, and in 2 cases of chronic epidermophytosis not listed in Table I, there has been some improvement in the athlete's foot. This is probably due to the 25 per cent propylene glycol in the ointment base which is somewhat fungicidal.

Four cases of acne vulgaris of the face have been treated with furacin soluble dressing. It has been found that the number of comedones and the number of acute pustules has been diminished greatly by the use of furacin soluble dressing once a day at bedtime.

Several cases not listed in Table I have been treated with furacin soluble dressing in an attempt to prevent any expected infection. In 2 patients who had a Torek operation, the scrotal-thigh incision was covered with furacin soluble dressing in the operating room, and no slough or infection occurred. In 2 patients who had a Mikulicz colostomy through an inguinal incision, the incision healed by early granulation even in the presence of fecal material.

In all cases, special attention was given to the effect of treatment on the base of the lesions and the effect on the discharge and odor. In these respects the following generalizations can be made:

The base of the lesions treated has shown no change in 14 of the 90 cases. In the majority of cases with secondary infection, the infection disappears almost at once, leaving a clean base. Granulations in the base of ulcers appear early, appear healthy and red, but do not tend to overgrow the skin edges. There is no retardation of the epithelization of these wounds by use of the dressing.

The discharge from a wound is lessened in the majority of cases, 79 of our 90. The discharge decreases in amount within 24 to 48 hours after the original use of the ointment. This diminution prevents the maceration of the wound by a purulent discharge.

The odor of foul wounds is improved within 24 hours after the use of furacin soluble dressing. The reduction in the odor is closely allied with reduction in the number of invading organisms. Particularly is the reduction of odor noted in the treatment of foul, draining stasis ulcers of the extremities.

Irritation. Comparison with other drugs. Fifteen of the patients treated with furacin soluble dressing had had local applications of

TABLE II.—CLINICAL SUSCEPTIBILITY OF STRAINS OF BACTERIA ISOLATED FROM LESIONS TO FURACIN SOLUBLE DRESSING MEASURED BY BACTERIOLOGICAL CULTURE RESULTS

Organism	Total No. strains	Total reduced		Total negative		Total not reduced		Total—No data
		No.	Per cent	No.	Per cent	No.	Per cent	
Staphylococcus aureus	29	14	93	12	80	1	6.6	14
Staphylococcus albus	35	21	87.5	14	58	3	12.5	11
Staphylococcus hemolyticus	25	13	92.9	8	57	1	7.1	11
Staphylococcus anhemolyticus	7	3	75	1	25	0	0	4
Pseudomonas pyocyanea	10	5	62.5	5	62.5	3	37.5	2
Proteus vulgaris	13	6	60	4	40	4	40	3
Escharichia coli	3	2	66.6	2	66.6	1	33.3	0
Aerobacter aerogenes	11	3	75	3	75	1	25	7
Diphtheroid	28	10	62.5	10	62.5	6	37.5	12
Aerobacter fecalis	4	4	100	4	100	0	0	0
Pseudomonas fluorescens	5	4	100	3	75	0	0	1
Micrococcus luteus	1	1	100	1	100	0	0	0
Micrococcus flavus	1	1	100	1	100	0	0	0
Total	172	87	81	68	63	20	19	65

sulfathiazole ointment 5 or 10 per cent for 1 to 2 weeks prior to their coming to us. In these patients the sulfathiazole ointment either showed no effect on the lesion or caused some type of local irritation. In all cases after discontinuance of the sulfa ointment and the application of furacin soluble dressing, there has been a marked improvement in the lesions.

Patch tests have been done on 30 patients by use of furacin soluble dressing, sulfathiazole ointment 5 per cent, and a tyrothricin ointment. In the 30 cases, there has been no reaction to furacin soluble dressing. There have been 4 patients who have shown a red, weeping, macular to papular area under the lesion treated with sulfathiazole ointment. Nine patients of the 30 have shown a marked edema and bulla formation under the patch test for tyrothricin ointment. This high incidence of skin reaction to tyrothricin ointment is probably due to the ointment base used. In our usual experience the reactions to tyrothricin ointment are fewer in number. This lack of reaction of the tissues to furacin soluble dressing is borne out well in the treatment of the 90 patients. In this series, only 2 patients developed any dermatitis at all. One patient developed a fine, red, papular rash under the area treated after 44 days' application of furacin soluble dressing. The other patient developed a similar rash after 8 days' application of furacin soluble dressing. In both cases, the rash disappeared within 48 hours after discontinuance of the ointment. In this respect, furacin soluble dressing appears to be superior to other ointments so far presented for local application.

BACTERIOLOGY

Culture findings. The lesions of the patients treated with furacin soluble dressing in this study were carefully cultured before and during treatment. Swabs from the lesions, pus, or body fluid were cultured aerobically and anaerobically on appropriate media. These samples were plated in a uniform manner so that rough estimations of the numbers of colonies produced could be made and by this method reduction as well as disappearance of the wound flora could be determined within the limits of error of the method.

As shown in Table II, column 1, 172 strains comprising 13 species of organisms were isolated. The gram-positive cocci and diphtheroids predominated appearing as 71 per cent of the total cultures. Among these were Staphylococcus aureus, Staphylococcus albus,

hemolytic streptococci and diphtheroids. The last named were not classified further as to species but grouped under the one general heading. Of the gram-negative flora encountered, Proteus vulgaris, Pseudomonas pyocyanea and Aerobacter aerogenes were most frequent. Surprisingly, only 3 strains of Escherichia coli were isolated. Except for this infrequent occurrence of Escherichia coli these findings are in good agreement with all reports on the pathogenic flora of civilian wounds and lesions.

Clinical susceptibility as measured by culture reduction. In Table II are also given the actual numbers and the percentage of the cultures isolated which showed a reduction in the number of colonies produced from the clinical material. This is shown in column 2. Column 3 shows the numbers and percentages of cultures which were completely negative and column 4, the number of cultures showing no change during the period of time which the cultures were followed. The last column presents the number of cultures which were not followed beyond the original isolation and identification either because the patient did not return or subsequent examinations showed the lesion healed.

The criticisms inherent in the procedure used in determining merely the reduction of the flora of lesions is clearly recognized, i.e. the type of lesion, the method of obtaining the samples, the presence of drug carried over in the sample and the plating technique. However, the data are presented in light of this criticism as an effort to present as careful and controlled a study as was possible under the conditions. Thus the findings in column 2 showing that 87 or 81 per cent of 107 cultures (total cultures minus those on which no data were available) are subject to the above criticisms as to their value in showing the effect of the drug treatment.

It is generally accepted, however, that negative cultures are of value in estimating the effect of treatment on the infecting agent. In this study, column 3 shows that of the 107 strains followed, 68 or 63 per cent became negative during treatment with furacin soluble dressing. An examination of the data showed that this action was accomplished in some cultures in as little as 24 hours while others required as long as 30 days for reversal. Further correlation of these figures with the clinical improvement in the lesions is not possible because of the presence of several organisms in any one patient, all having variable susceptibility. Thus, in some cases, healing of the lesion progressed rapidly with the disappearance of one species originally present, although another might remain without any noticeable effect even after completion of treatment.

In column 4 are given the numbers and percentages of strains which showed no change in the quantity of colonies produced by succeeding clinical samples during the course of treatment, and thus labeled resistant or nonsusceptible to furacin. It is only fair to point out, however, that in some cases, the period of time on which such a conclusion is based is relatively short and may not represent a fair test of the drug. For example, many strains were exposed to the drug for only 3 to 4 days, at which time the lesions were improved clinically or had healed sufficiently to stop treatment, yet the organism remained. In addition, many of these cultures were found to be susceptible to furacin when tested *in vitro*.

As a group, the gram-negative species showed a larger number of nonsusceptible strains than the gram-positive group with the exception of the diphtheroids. Proteus (40%), Bacillus pyocyaneus (37.5%), Escherichia coli (33.3%), and Aerobacter aerogenes (25%), were resistant in the order given. In the gram-positive group only the diphtheroids showed a similar resistance. The pyogenic cocci, on the other hand, were on the whole most susceptible. Resistance in this group was as follows: Diphtheroids (37.5%), Staphylococcus albus (12.5%), Staphylococcus hemolyticus (7.1%), Staphylococcus aureus (6.6%), Staphylococcus anhemolyticus (0).

It is quite possible that the high percentage of resistance in the diphtheroid group may be due to lack of sufficient exposure to the drug because of a limited treatment period, and perhaps to the existence in this group of a particular species which is more resistant than others.

Susceptibility in vitro. Ninety-seven strains of the cultures isolated in this study were examined *in vitro* for their susceptibility to furacin soluble dressing, furacin (1–500) in carbowax and water and to the base alone (carbowaxes 1500 and 4000 and propylene glycol). In this way, the relative merits of furacin and the base ingredients as antibacterial agents could be evaluated.

The tests were done by a modification of the standard F. D. A. cup plate test, the medium employed being the only variation from the standard procedure. Brain-heart infusion agar (difco) was substituted because of its ability to produce better growth of streptococci and diphtheroids. All zones of inhibition measuring 1.0 millimeter or more were considered proof of antibacterial action.

The results are listed in Table III. It is pertinent to point out that the base itself minus furacin showed an antibacterial effect on only 4 strains out of 97, while furacin soluble dressing affected 93 of the total and furacin itself 89. The discrepancy in the latter two figures is due to a finding of 1.0 millimeter for furacin soluble dressing and zero for furacin with several strains.

Only two groups, Pseudomonas pyocyanea and Staphylococcus albus showed strains resistant to furacin soluble dressing, *in vitro*, susceptibility being 83 and 89.4 per cent, respectively. With furacin in carbowax and water these two groups were 58.3 and 84.2 per cent susceptible respectively. Pseudomonas flourescens group were 100 per cent susceptible to furacin soluble dressing but only 87.5 per cent susceptible to furacin. All other groups were 100 per cent susceptible.

The results obtained on the clinical and *in vitro* susceptibility of Pseudomonas pyocyanea are surprising in view of the previous reported facts (2, 4) that this organism is resistant *in vitro* to the maximum aqueous concentration of furacin possible (1–5000). Also Snyder, Kiehn, and Christopherson reported that this organism was not susceptible clinically or *in vitro*.

Several factors may explain these apparent discrepancies. Clinically, pyocyaneus usually appeared in combination with one or more organisms. In many cases, these latter were susceptible and as they disappeared an apparent symbiosis with pyocyaneus was destroyed so that it perhaps disappeared because of the natural body processes, and only secondarily as the result of the drug.

TABLE III.—STRAIN SUSCEPTIBILITY IN VITRO TO FURACIN SOLUBLE DRESSING, FURACIN AND BASE

Organism	No. strains isolated	Per cent susceptible furacin soluble dressing	(Zone of 1.0 mm. or more)	
			Furacin	Base alone
Pseudomonas pyocyanea	12	83.0	58.3	16.6
Staphylococcus aureus	14	100.0	100.0	0
Staphylococcus albus	19	89.4	84.2	0
Diphtheroids	17	100.0	100.0	0
Staphylococcus hemolyticus	5	100.0	100.0	0
Proteus vulgaris	8	100.0	100.0	12.5
Pseudomonas fluorescens	8	100.0	87.5	0
Aerobacter fecalis	5	100.0	100.0	20.0
Aerobacter aerogenes	6	100.0	100.0	0
Micrococcus	2	100.0	100.0	0
Staphylococcus anhemolyticus	1	100.0	100.0	0
Friedlaender's bacillus	1	100.0	100.0	0
Total	97			

The *in vitro* susceptibility may be the result of the ten-fold increase in concentration available in furacin soluble dressing over the tests run in aqueous solution. Also, it was noted that the majority of zones of inhibition produced in the tests on Pseudomonas pyocyanea were about 1.0 millimeter in size, the minimum required for a rating of susceptibility, whereas all zones on staphylococci, for example, measured from 5 to 10 millimeters. It is therefore probable that the variation occurring in strain resistance in this species, causes the appearance of some strains susceptible to 0.2 per cent of the drug. However, Pseudomonas pyocyanea probably should not be listed as susceptible until more data are available.

CONCLUSION

The usefulness of furacin soluble dressing in the treatment of superficial infection has been fairly well established. It is known that the drug must reach the invading organism to cause any bacteriostatic or bactericidal effect.

Furacin soluble dressing does not remove the need for adequate surgery. The outstanding property of this ointment is the immediate reduction of the odor and drainage from a wound. There has been no evidence that the ointment retards or prevents epithelization or granulation of a wound. In fact, the wounds appear healthy almost at once. The incidence of local skin reactions has been very low, 2 in 90. The improvement in the appearance of a lesion has followed closely the decrease in the number of organisms plated out on culture.

It has been interesting to observe that the clinical improvement has paralleled the disappearance of one or more of the infecting organisms from the wound. The lesions have healed well when the symbiosis of the organisms has been broken up. The gram-positive and gram-negative species usually seen in surface infections showed a high degree of susceptibility to furacin, clinically and *in vitro*.

SUMMARY

1. Ninety patients with local infections have been treated with a new ointment—furacin soluble dressing.

2. The ointment has been found useful in the treatment of superficial infections.

3. There has been a very low incidence of skin reactions to the drug (2 in 90).

4. The ointment must reach the organisms to obtain a bacteriostatic effect.

5. Clinically, granulation tissue is not retarded in its growth.

6. Epithelization of the wound is not inhibited clinically.

7. The ointment will decrease rapidly the odor and drainage from a wound.

8. Furacin soluble dressing has shown less skin irritation or reaction than has sulfathiazole ointment or tyrothricin ointment to patch testing.

9. Culture results show a high degree of susceptibility to the drug of the gram-positive and the gram-negative flora which was encountered.

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EDITORIALS

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PROGRESS IN THE SURGICAL TREATMENT OF CARCINOMA OF THE ESOPHAGUS

THERE is an interesting parallelism in the evolution of the surgical treatment of carcinoma occurring in various organs of the body. After centuries of hopeless inaccessibility, each important anatomical region has at last been brought within the reach of the surgeon's art. At first the attempts to extirpate the dread disease in each organ have met with failure and disappointment because of the imperfection of technical methods and the fact that the problem has usually been given over to the surgeon at first with reluctance and suspicion. Establishment of the correct diagnosis has often been delayed and an attitude of hopelessness has been assumed by the physician.

Various attempts to extirpate a cancer-bearing segment of the esophagus were made in the early years of this century. Notable among these was the work of Torek who performed the first successful esophagectomy in 1912. But although the concept of the procedure was clear, its performance was hampered by a lag in the technical developments needed to make the procedure sufficiently safe to justify its use routinely in the treatment of the disease. The passage of years was required for the realization of this goal, as a result of improvements in the administration of the anesthetic, the conduct of the operation, and the general preparation and subsequent care of the patient. It has therefore fallen to a new generation of surgeons to accomplish what was foreseen by the pioneers.

Although a few satisfying results have followed the use of the Torek operation, the time has come to abandon this procedure because it is notoriously inadequate as a method of palliation and inefficient as a method of cure. During the last few years it has become possible to perform an operation which more nearly approaches the ideal of removing the esophagus and enough of the regional lymph nodes to afford a reasonable prospect of effecting a cure, and which at the same time provides excellent palliation by restoring the continuity of the alimentary canal. This procedure consists of a radical excision of a large segment of the esophagus, often including a portion of the cardiac end of the stomach, and of the majority of the regional lymph nodes to which metastases first go. It is completed by performing an esophagogastric anastomosis within the thorax. If the growth happens to be a high one, the anastomosis can be made in the very apex of the chest.

The advantages of this operation are obvious. It has been used in a sufficiently large number of cases to know that the operative

mortality is low enough to make the procedure practicable and to prove without question that it provides the most acceptable degree of palliation. This is particularly clear because it is most unusual for a recurrence of the disease to develop at the anastomotic stoma, so that the patient continues to swallow without obstruction as long as he may live.

From the standpoint of end results, the procedure is yet too new to allow accurate conclusions. There are only a few patients who have been operated upon more than five years, and relatively few more than three years. An encouraging beginning has been made, however, and when we consider the progress which has already been made in the treatment of carcinoma of other organs, the future prospects of patients with carcinoma of the esophagus are indeed hopeful.

RICHARD H. SWEET.

FRACTURES OF THE OS CALCIS

FEW fractures present so many and such difficult problems in their management as do fractures of the os calcis. The great variation in the severity of the injury, the frequent involvement of the subtalar joint and the technicalities involved in the reduction of the fracture combine to make this a major treatment problem in the field of fracture surgery.

Experience with fractures of the os calcis has been enormously broadened by the recent war. Land mines (both antitank and antipersonnel, but especially the former) and ship sinkings by mines and torpedoes, made fracture of the os calcis a frequent injury with features so distinctive as to create almost a new kind of fracture characteristic of this war. Such war fractures, caused when the floors of vehicles and the decks of ships were driven up with great force against the heel, were of great severity; the os calcis shattered into many fragments which were grossly displaced. The injury was explosive in its effect upon the bone, and the fracture often was compound. Effective early treatment was handicapped by the exigencies of forward-area surgery, by the problems of an open wound, by circulatory embarrassment from swelling and trauma, and by transportation problems which made it impossible to segregate them for special treatment. Many came to amputation. Feet which escaped amputation presented major problems in reconstructive surgery, with little hope of restoration of the tarsus to normal shape and function. So severe were war fractures of the os calcis that they constitute a group almost by themselves, related only distantly to the fractures of the os calcis of civil life.

No fracture illustrates better than does fracture of the os calcis the truth of the axiom that, in fractures, early treatment determines irrevocably the result in terms of structure and function. There is a brief and early period in which the maximum can be accomplished by treatment. If this moment of opportunity is allowed to pass by adopting a policy of "wait and see," what can be accomplished by later treatment will never be as satisfactory. In fractures of the os calcis this period is short, for the cancellous fragments of the bone quickly cement themselves together into a mass which resists molding.

For the occasional surgeon the initial injury may seem a deceptively simple problem. The external appearance of the foot is changed little more than can be accounted for by the soft tissue swelling, and the roentgenograms may be imperfect or difficult to interpret. The loss of function which will result from the injury is learned only by painful experience.

This is a fracture problem in which the services of an experienced and expert fracture surgeon are needed, and these should be sought in the early stage of treatment.

Imperfect or poor results after fractures of the os calcis are frequent and the degree of functional disablement is greater than might be expected from the magnitude of the fracture. A stiff, painful foot is the common end-result and is caused by involvement of the subtalar joint by the fracture. As is the case with other intra-articular fractures, joint function is certain to be impaired and painful if the fractured articular surface is not meticulously restored to normal position. Even the attainment of such perfect reduction of the fracture does not provide perfect assurance of good function. Other factors may combine to limit joint movement and make it painful. Of these the most important, but at the same time the least recognized, is avascular necrosis of a bone fragment carrying articular cartilage which has been isolated from its surrounding contacts by fracture fissures. When this occurs in such a manner as to deprive the fragment of its blood supply, even the most perfect restoration of position will not ensure perfect joint function. During the period of avascular necrosis the articular cartilage dies in whole or in part and is never perfectly restored. There is left a rough patch on the articulation which damages the joint with every movement.

Difficulties of treatment and imperfection of results have led certain surgeons deliberately to advocate that no active treatment be undertaken for fractures of the os calcis, merely fixation in plaster in the position of the injury until union has occurred. It is argued that such treatment is simple, can be carried out by any one and that the results are no more imperfect than those obtained from more elaborate forms of treatment.

Such a policy of "studied neglect" is a confession of defeat. There is little to support its advocacy save its simplicity. Os calcis fractures like all other fractures will yield the best results when the fracture fragments are most perfectly reduced. This is especially true in intra-articular fractures. Though this may be difficult to attain in fractures of the os calcis, it is an ideal to be aimed at. The realization that it is difficult is the first step to devising effective measures of treatment. Bochler emphasized the value of traction to secure accurate reduction of the fragments. The use of traction can be broadened far beyond Bochler's concept with advantage. All other mechanical aids should also be used.

Because of the frequent involvement of the subtalar joint, it should be recognized that stiffness and painful function of this joint may result even when good reduction has been secured. Arthrodesis is a valuable form of treatment for this and should be utilized more frequently than it now is. Nearly every patient whose fracture shows serious fragmentation of the articular surface of the posterior facet of the calcaneus would be the better for arthrodesis. The suitable cases should be selected and the patients operated upon at an early date.

It is probable that for the extremely severe fractures with great comminution and great separation of the fragments, as in war fractures, the removal of the whole bone as advocated by Pridie may prove to be a simple and reasonably satisfactory solution of a difficult problem.

The frequent occurrence of fractures of the os calcis in industry, the complexity of the problems involved in treatment and the importance of the end-result make them a challenge to stimulate improved measures of therapy.

ROBERT I. HARRIS.

THE SURGEON'S LIBRARY

THE BOOK SHELF

THE INTERDEPENDENCE OF ARTIST AND ANATOMIST

VERA MOREL, New Orleans, Louisiana

FORTUNATE is the medical illustrator whose workshop adjoins a medical library. Within the restful quiet of book-filled walls, the eye and the mind may derive abundant and profitable pleasure from the study of plates that enrich and elucidate many of the treasured classical works. Present-day students and artists should be encouraged to "take time out" for browsing among historic volumes, thereby discovering and knowing intimately the illustrations of the early masters to whom we are so deeply indebted.

Contemplation of great works provides first surprises and interest, and as they become familiar there arises a desire to shift our attention to the individuals who created them. To learn something of their personalities, their surroundings, their problems, what they thought and felt and, mainly, how they worked together—this becomes a fascinating pursuit.

Collaboration and interdependence always have been essential to the peculiar requirements of medical illustration. The production of a medical book demands the concerted efforts of many minds and many hands, a co-ordination of crafts that are diverse yet closely interrelated. The artist is dependent upon guidance and in turn exchanges an ability to transfer his observations with accuracy, clearness, and technical proficiency. Possibly with the exception of the extraordinary genius, Leonardo da Vinci, few artists have become scientists in the true sense of the word, and while there have been medical men who were creditable illustrators only rarely did they attain greatness as artists.

How did the artist and the scientist work together; what was the attitude of one toward the other; was there friction and clash, or harmony and possibly deep friendship? Expressions of warm admiration and gratitude for the contributions made by illustrators and engravers have been recorded in the writings and biographies of medical men. In contrast, others have been silent, even secretive, and unsigned illustrations in some important anatomical works have brought about spirited controversies, speculation, and an abundance of literature. Artists seem to have been strangely inarticulate about themselves.

Although there exists no published work of the brilliant young Veronese patrician, Marc Antonio della Torre (1478–1512?) and no book of illustrated anatomy was ever completed by his friend and countryman, Leonardo da Vinci (1452–1519), it is known that the two scholars were associated for a brief period of time. The influence of one upon the other is a matter of conjecture. Leonardo's passion for the study of anatomy long antedated his meeting in the year 1506 with della Torre who had come to establish a chair of anatomy at the University of Pavia. Giorgi Vasari (1511–1571), art historian of Italy, records that della Torre was "one of the first to throw true light upon anatomy which up to that time had been plunged in the almost total darkness of ignorance. In this he was wonderfully aided by the talent and labour of Leonardo, who made a book drawn with red crayon annotated with the pen (of the subjects which he dissected with his own hand and drew with the greatest diligence)." Vasari had visited Milan in the year 1566 and met Francesco Melzi to whom Leonardo had bequeathed his fugitive manuscripts and precious drawings which were destined to be scattered, hidden, and forgotten for two centuries.

One of Leonardo's later biographers, Edward McCurdy, writes: "Leonardo was della Torre's senior by almost thirty years and Müntz supposed that he occupied the position of master with a pupil in these researches; others have supposed the position reversed . . . It seems natural that in the case of the two rare intellects working in unison toward a common purpose there would be neither master or pupil in the ordinary sense of the terms."

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While Leonardo's notebooks record his thoughts and observations, little of his personal life is revealed therein, and no mention made of della Torre who died, aged 31, in the little epidemic-stricken town of Riva di Trento in the year 1512. The sudden death of the popular young master of anatomy may have caused Leonardo to abandon the plan he entertained for a comprehensive work of one hundred and twenty books on anatomy, as he had written that "In this winter (1510) I believe I can send off this whole anatomy."

Any attempt to evaluate Leonardo's contributions to anatomy is beyond the intent of this study and difficult would it be to measure his certain influence upon modern medical illustration. Many of us have been inspired by the zeal and intense devotion he gave to anatomical science as well as by the intellectual force and unparalleled beauty of his impromptu anatomical drawings. "Whatever he draws," writes Rachel Annand Taylor, "the effect of magical disquiet is Leonardo's enduring gift . . . a stir and expectation in the mind, a pulse and apprehension in the blood."

Would that we knew more of the relationship between the compassionate physician della Torre and the usually aloof Leonardo who has been styled the true founder of iconographic and physiologic anatomy. Both investigators embodied the exploratory spirit of the Italian Renaissance, that period of brilliant learning in art, literature, and science when observation assumed its rights and anatomy became articulate through pictures.

Meager and confusing are the facts concerning the artist or artists who worked with Andreas Vesalius (1514–1564) in the creation of his impressive and revolutionary publications. Many historians have been attracted by the romantic and enigmatical character of the young anatomist from Brussels who at the age of twenty-eight attained the summit of scientific greatness. In *De Humani corporis fabrica Libri septem* (1543), the structure of the human body was properly portrayed for the first time. Traditional methods of teaching anatomical science were supplanted by independent investigation and drawings after nature. As to the real hero of the *Fabrica*, opinions vary. Vesalius has been credited with the magnificent drawings as well as with their accompanying descriptive text. However, in more recent years cudgels have been taken up in defense of Jan Stephan van Calcar (1499–1547) who had come down from Flanders to work under the great painter Titian in Venice where he acquired a mastery of the then new tridimensional effect achieved by the use of but two dimensions. For many years the beautiful woodcuts of the *Fabrica*

were thought to be the work of Titian, so able a follower of the master was Calcar. Christoforo Coriolano also was credited with the unsigned drawings, and it has been suggested that the influence of Leonardo is reflected in these illustrations, but there is no support for this supposition. Nor is it wise to quote from Vasari's second edition of his *Lives of the Painters* (1568), wherein Calcar is mentioned, for, as the historian Charles Singer points out, Vasari's account does not aid in establishing "the reality or the degree of Calcar's participation in the *Fabrica*."

Recently a handbook of Vesaliana has been provided in *The Bio-Bibliography of Andreas Vesalius* (1943) by the late surgeon and bibliophile, Harvey Cushing, who devoted forty years to the collection and study of all data pertaining to Vesalius. Cushing says of the *Fabrica* that as a book it "has probably been more admired and less read than any publication of equal significance in the history of science." He gives the following lines of evidence to establish Calcar's association with Vesalius: "(1) the allusion to Stephen in the introduction to the *Tabulae Sex;* (2) the occurrence of his name in the colophon of the last plate of the same work; and (3) the signed figure of the young artist in the engraved frontispiece of the *Fabrica*, evidently a selfportrait with the figure, book in hand, overseeing the dissection. There is

a signed *croquis* of the *Fabrica* title-page bearing the name of Calcar. This fourth line of evidence is possibly more presumptive, but taken in association with the first three, it serves further to confirm their close relationship."

In the *Venesection Epistle* (1539) Vesalius writes his patron, the physician Nicolaus Florenas of Brussels: "We have tried to make out a scheme of the dissections of this present year in the most convenient manner possible, but in view of the great crowd of spectators it proved altogether impossible to complete it," and concludes: "So if I have a number of suitable cadavers, and Joannes Stephanus (Calcar) the most admirable artist of our time does not refuse his assistance, I shall not run away from my task." At another time Vesalius refers to Calcar's ability, but the artist's name is omitted from the illustrations of the *Fabrica*. Whether this omission was for reason of ill-feeling, envy, or mere inadvertence remains a perplexing puzzle.

Undoubtedly, the impetuous Vesalius was a driving master and became impatient and grieved over any delay on the part of his coworkers. Calcar and other assistants may have preferred the pleasantness of ivory towers to the turmoil of the dissection scene where the dynamic young anatomist held the spectacular anatomical demonstrations at Padua which are so graphically portrayed in the frontispiece of the *Fabrica*. Vesalius refers to his own ability as a draftsman and three drawings of the six anatomical tables (1538) are by his hand, but the plates of the *Fabrica* are unmistakably the work of a trained and skilled artist who transcribed with fidelity and beauty what he observed and comprehended.

Despite personal difficulties that may have existed and the great amount of labor involved in the preparation of a comprehensive systematic anatomy in the space of a few years, the work reached completion and immortality. While no written account is available of the manner in which Vesalius and Calcar worked together, the *Fabrica* remains a perpetual source of inspiration and of joy, and may be accepted as a glorious and certain instance of artist-anatomist teamwork and interdependence, although uncertainty as to the identity of the artist may still exist.

No name is signed to the copperplates in the early works of Guilo Casserio (Casserius) (1552–1616), but the following passage from the writings of Casserius is cited by Choulant: "I observed this muscle in the year 1593, on the seventh of March and immediately had it drawn for everlasting memory by that distinguished man Joseph Maurer, the German artist, who was at that time living in my household for the purpose of painting anatomic illustration." Casserius died before his ambitious anatomical projects were completed. In later editions of his works the drawings bore the name of Odoardo Fialetti and Choulant adds that "owing to the correctness of Casserius' plates and their tasteful arrangement and the beauty of their technical execution, they mark a new era in anatomic representation . . . and have become models for anatomic illustrations in copper."

Refreshing and illuminating are the accounts of Bernard Siegfried Albinus (1697–1770) whose investigations established an entirely new approach to illustrative anatomy. Albinus, professor of anatomy at Leyden from the age of twenty-nine until his death, was an able draftsman and had keen appreciation of artistic ability in others. He secured the services of the most skilled artists and expended huge sums of money for the illustrations in his many works. We are told that he was assisted by the talented Jan Wandelaer (1690–1759) of Amsterdam, who had previously worked for Frederick Ruysche and Arent Cant.

Albinus describes in detail his methods of illustration and tells of the extra and occasionally burdensome effort required to train artists, stressing the fact that his illustrator reproduced nothing

that was not first thoroughly understood. He gives accounts of the various ingenious contraptions devised by himself for drawing of skeletons and musclemen in exact proportions. Of Wandelaer he writes: "And so he had to be trained and guided and practically directed by me as if I were myself making the pictures, using him as a tool." Upon another occasion he remarks: "I have often wondered at his spirit, his patience, and resolution; he is moreover ardent and never without a certain impetuous eagerness of effort."

Again he writes: "He (Wandelaer) has reproduced everything with truth and accuracy and with a marvelous refinement of skill. He has reproduced all the smallest details and what is more difficult, the very appearance, in so far as that art could. Still better is the fact that he draws beautifully and, what is even more important, draws the pictures on copper after the objects themselves." The great amount of attention that Albinus gave to the production of his illustrations was well repaid in the unparalleled results that he attained. Every word, and there are many, that he has written is worthy of study and remembrance, for he brings in strong relief the necessity for close co-operation between author and illustrator.

We have a fondness for the extraordinary personality of Samuel Thomas von Soemmerring (1755–1830) who was a devoted follower of the great teacher, Albinus. From the days of his boyhood, Soemmerring was skillful with his pen, both in drawing and in writing. His accounts of interesting travels, of friendships formed with noted medical men in other countries, and of personal struggles, make stimulating reading. Theodore Best writes: "That his careful transfer of his observations and experiences into writing and sketches no doubt was a fundamental factor in his keen observation, accurate descriptions, and clear illustrations later.

Soemmerring was fortunate to find Christian Koeck, a young artist, employed as a stucco-worker and model-maker in an art shop near the University of Mainz, who developed into an outstanding medical illustrator. "He turned out admirable illustrations, unexcelled in purity, certainty, and truthfulness," writes Choulant . . . But Koeck caused him a great deal of trouble, especially when he went to Moscow, where he was very unfortunate and could only return to Munich in 1809, after great pecuniary sacrifices on Soemmerring's part." In Frankfort, as in other cities, Koeck lived with Soemmerring. He died in 1818.

Here also is an anatomist and an artist who left us record of personal experiences in the preparation of graphic representations. Among Koeck's most beautiful drawings are those in Soemmerring's treatise on the eye. In the preface of this book, the author wrote: "therefore I begged the artist to try his best to combine the greatest accuracy of individual details with the strongest retention of the whole, so that the finished product would produce the proper impression both from near and distant view. . . . Truly accurate sketching costs no more effort than incorrect! Does it not, for example, cost the same effort whether I picture the hair of the eyebrow slanting, as they lie in nature, or horizontal, as one finds them pictured so often.

The story of how Soemmerring created a female counterpart to the perfect representation of Albinus' male skeleton is a familiar one, and it is interesting to surmise the extent of the mutual assistance required and the dependence of artist and author in this particularly difficult task. After many comparative studies the completed drawing was, as Choulant says, "necessarily an idealized one, since it had to represent not an individual form but the most beautiful form as it was imagined to exist in life." We quote the same authority who explains the strong and lasting influence of

Soemmerring's illustrations in these words "They displaced all the repulsive, unaesthetic, and unnatural features so often prominent in earlier anatomic representations by the substitution of incomparably better ones."

Another great anatomist, William Hunter (1718–1783), contributed great care and great sums of money in the production of his works. His volume of the *Anatomia uteri humani gravida* (1774) from the press of Joannes Baskerville, represents the work of many artists and many engravers. In the preface of this beautiful volume illustrated by talented men, including the famous Riemsdijk, are the following words written by John Hunter, the famous brother of the author: "He owes much likewise to the ingenious artists who made the drawings and engravings; and particularly to Mr. Strange not only for having by his hand secured a sort of immortality to two of the plates, but for having given his advice and assistance in every part with a steady and disinterested friendship." Sir Robert Strange was one of the many engravers contributing to the beauty of Hunter's great work.

Instances of the reciprocal relationships that existed between other anatomists and their artist-coworkers may be recited, but we are eager to mention an example that is near and familiar to contemporary medical illustrators. This is the association of a group of illustrious medical men at Johns Hopkins University with three talented artists who left their studios in Europe to come to America just before the turn of the past century. Max Brödel (1870–1941), who was the first to arrive (1894), has been titled "the greatest medical illustrator who has ever lived" by his friend and coworker, Dr. Thomas A. Cullen.

Upon the occasion of the seventy-fifth birthday of Dr. Howard A. Kelly (1858–1943), Max Brödel spoke and from this address we have taken the following words that relate to our subject: "He (Dr. Kelly) had a way of making little modest outline sketches when he explained his operative procedure to his illustrators. There were three of us now, Hermann Becker came in 1895, August Horn in 1898. Dr. Kelly had endless patience with us. He invented diagrams to show variations of form and relationship, motion, pressure, tension, rupture, the development of a pathologic process, the sequence of operative steps, the placing of ligatures, sutures, etc.; in short, every clinical phenomenon, every operative procedure flowed in simple, eloquent lines from the end of his pencil. Few medical men can do that. What if the work was not correct; it did not matter, the spirit was there. We understood his diagrams; they were eloquent. In this way Dr. Kelly taught his artist the secret of the correct conception of an illustration, which is the basis of all creative drawing. . . . This is one great debt we owe Dr. Kelly." Of another debt, Max Brödel continued: "Dr. Kelly always permitted the artists to make original investigations to clear up the obscure point. That meant temporary cessation of illustrative output until the question could be answered. . . . Few authors of medical books will do that. Without his sympathetic attitude we could not have learned our trade so well."

Through the vision and effort of Dr. Cullen, the opportunity to aid other artists was provided Max Brödel when the first school in the world for training medical artists was established at Johns Hopkins with Brödel as its director. It is significant that the fame of this modest artist and teacher will endure not alone because of his contributions to education and to art, but because his spirit was an investigative one and he keenly appreciated the need for close co-operation between author and artist.

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REVIEWS OF NEW BOOKS

THE fourth edition of Key and Conwell's *The Management of Fractures, Dislocations, and Sprains*[1] has the same physical appearance as the third edition, but many new illustrations have been added and older ones have been deleted. The book has been brought up to date and experiences gained by many workers during World War II have been incorporated.

The general principles of débridement, chemotherapy, and immediate internal fixation of fractures are aptly discussed and briefly presented in a readily understandable style. The chapters which are devoted to workmen's compensation laws and medicolegal aspects of fracture cases are well worth studying.

The discussions of fracture of the skull and brain trauma and fractures of the jaws and face are well presented by competent specialists in the fields mentioned.

The reviewer wonders whether the illustrations of the use of Kirschner wire traction through the distal third of the humerus and ulna for skeletal traction in the elbow region may lead inexperienced men who will be guided by this excellent book to attempt a method which requires skill, experience, and judgment. A more lengthy discussion of its dangers and perhaps an illustration of "picture hook" traction of the olecranon, as used by Cubbins for years, might help to diminish the risk associated with this procedure.

The authors are to be congratulated on maintaining the excellent standard of this work and for keeping the material abreast of the times. It is well worth study by student, general practitioner, and specialist.

CARLO SCUDERI.

THE influx of women into industry which began during the recent war has created a need for the book entitled *Women in Industry; their Health and Efficiency*[2] by Dr. Baetjer who has arranged in orderly fashion pertinent information gleaned from the recent medical literature.

The following subjects which are covered in this work indicate its scope: the ability of women to work; the types and conditions of work for women; sick absenteeism among women employees; accidental injuries to working women; occupational disease; gynecological and obstetrical problems associated with the employment of women; mortality and fertility of women in relation to occupation. In a single chapter Dr. Baetjer helpfully summarizes the above subject matter and arrives at some logical conclusions. The appendix lists some useful facts including labor laws for women, and the bibliography is most complete.

In my opinion this book is of value to all physicians and a "must" for gynecologists and for those engaged in industrial medicine and surgery.

F. L. SMITH.

THE work entitled *Le fibro myome uterin* by J. Ducuing[3] is based on 1300 cases, personally observed, of which 547 had not been previously published. The illustrations consist of many gross and photomicrographs, as well as a considerable number of line drawings.

The importance of the book lies in the author's vigorous championing of radiation therapy in preference to surgery in the treatment, in general, of fibromyomas. In a series of 434 cases, whose management he reports in detail, 74 cases were treated surgically, and 360 cases by radiation. The author states that he realizes the ideas which he defends on radiotherapy of fibromas have provoked much criticism, especially from surgeons. He attacks in detail the conclusions of the French Surgical Congress of 1924 in which, on the treatment of fibroids, a minor place was given to radiotherapy and a major one to surgery.

The book presents also many and complex aspects of the subject, such as surgery, endocrinology, jurisprudence, experimentation, physiology, and pathological anatomy. In Chapters I through VI the author presents a number of composite studies including age groups affected, menarche and menopause, fibroids and pregnancy, and gross characteristics of fibromyomas. In Chapter VII he considers the present state of research and after a review of anatomy and physiology, he discusses the fibroblast, the muscle fiber in the fibromatous uterus, the sclerous uterus, and the uterine mucosa. Circulatory relationships in myomas are shown by photographs of corrosion specimens. A note on the physiology of the femal genital cycle, on the sex hormones, and on the synchronization of the menstrual and ovulatory cycles immediately precedes the discussion of the pathogenesis and mechanism of bleeding associated with fibroids. Treatment, indications, and techniques are reviewed in Chapter X. Surgical conservation of the ovary is definitely inferior in the author's opinion to radiation castration. Operative procedures on the uterus are reviewed by a series of line drawings. The author emphasizes postoperative embolism while minimizing the possibility of any late

[1] THE MANAGEMENT OF FRACTURES, DISLOCATIONS, AND SPRAINS. By John Albert Key, B.S., M.D., and H. Earle Conwell, M.D., F.A.C.S. 4th ed. St. Louis: The C. V. Mosby Co., 1946.

[2] WOMEN IN INDUSTRY; THEIR HEALTH AND EFFICIENCY. Issued under the Auspices of the Division of Medical Sciences and the Division of Engineering and Industrial Research of the National Research Council. By Anna M. Baetjer, Sc.D. Philadelphia and London: W. B. Saunders Co., 1946.

[3] LE FIBRO MYOME UTERIN. By J. Ducuing. Paris: Masson et Cie, Editeurs, 1946.

or incidental damage consequent to radiation. Radiation effects on bowel and bladder are not emphasized. An alphabetical subject index and author index, a list of the figures with their titles, and a table of contents are appended.

VICTOIRE LESPINASSE.

UNDER the editorial supervision of Doctor Fleming, *Penicillin*[1] represents a summary of the present state of knowledge regarding penicillin and contains a series of contributions by twenty-eight experienced and eminent men in Great Britain, who present their views on various aspects of penicillin therapy. The first few chapters deal with the general aspects of penicillin, including its history, development, chemistry, pharmacy, pharmacology, bacteriological control, and various methods of administration. The clinical portion of the book is not merely a résumé of the work done with penicillin, but is a concise digest of the practical experience in penicillin therapy, as summarized by these representative specialists. It is a veritable encyclopedia of the indications, limitations, and accepted methods of treatment with penicillin. In addition to the purely medical sections, there are chapters on the use of penicillin in dental and veterinary surgery. For those interested in more detailed information on a particular subject, there is a representative and annotated bibliography at the end of each chapter. It is authoritative, clear, concise, well written, adequately illustrated, and easily read. Although there is a certain amount of reduplication and some difference of opinion between the various authors, this should help the reader to obtain a broader viewpoint. The subjects are treated in sufficient detail to make this book valuable to practitioners, specialists, and students alike.

W. A. ALTEMEIER.

AFTER preliminary training under Doctors Henry and Richard Finochietto, the author of *Tumores; broncogenicos; la cirugia toracica en Los Estados Unidos de Norte America*[2] spend the period from July 1940 to October 1942 in the United States, devoting his time to the study of thoracic surgery, as exhibited in the major North American centers for such work. Most of his study in the United States was centered in St. Louis and upon the service of Dr. Evarts A. Graham.

His utilization of this period of time must have been exemplary because he devoted it not only to the actual day by day management of patients, but also to the detailed study of the accumulated wealth of clinical material available there, and to a minute investigation of the teaching methods and organization of the service.

This volume, published in a monograph, comprising some 450 pages, is divided into two main parts. The first is a review of bronchogenic tumors and the second a survey of thoracic surgery in the United States.

The portion on bronchogenic tumors is an exhaustive analysis of bronchogenic carcinoma and the so called mixed tumors of lung. The clinical data are obtained from the case records in Barnes Hospital. In the first five chapters he reviews carcinoma and considers all phases of the problem—pathologic, clinical, and therapeutic. Many and varied statistical analyses are included, based on 264 histologically confirmed cases and on 52 consecutive pneumonectomies, representing a period of 10 years (1932–1941). Of the 52 patients subjected to pneumonectomy, 15 were living and well between 6 months and 9 years and 4 months following operation.

Operative technique is outlined and the various techniques utilized during this period, much of which was evolutionary and early in the history of pneumonectomy, are contrasted. The comparison of results between mass ligation and individual ligation techniques, for example, is interesting. Many other such analyses are undertaken. A bibliography of 173 references to the world literature is appended to the chapters dealing with carcinoma.

Chapter VI is a discussion of mixed tumors of the lung.

The second part of the monograph takes up the scheme of teaching thoracic surgery in medical centers in the United States, the detailed organization of thoracic surgical services and finally the organizational set-up of tuberculosis sanatoria, based on Koch Hospital in St. Louis, Mo.

In the foreword by Dr. Evarts A. Graham, fitting tribute is paid the enterprise of such young surgeons seeking to broaden their experience by prolonged periods of study in this country. He briefly traces the evolution of thoracic surgery and supplements the clinical data of the author by indicating that by 1945, the number of pneumonectomies has risen to 157, whereas the mortality has fallen to 15 per cent.

This volume forms a very complete presentation and an analysis of a significant number of clinical records.

HIRAM T. LANGSTON.

THE monograph entitled *Traitement chirurgical du cancer du rectum*[3] represents ten years' work by the author on several hundred cases of carcinoma of the rectum. It considers only carcinoma of the rectum, not carcinoma of the sigmoid or pelvic colon. The author analyzes his cases and methods and compares them with the reported results of the leading surgeons in the rest of the world.

The work is a practical one and includes only enough anatomy to illustrate and show why certain procedures are adopted and others not. The author discusses and critically evaluates all methods of rectal removal: abdominal, sacral, perineal, and their various combinations with and without removal of

[1] PENICILLIN; ITS PRACTICAL APPLICATION. Under the general editorship of Professor Sir Alexander Fleming. Philadelphia: The Blakiston Co., 1946.

[2] TUMORES BRONCOGENICOS; LA CIRUGIA TORACICA EN LOS ESTADOS UNIDOS DE NORTE AMERICA. By Dr. Hernan D. Aguilar. Buenos Aires: "El Ateneo," 1946.

[3] TRAITEMENT CHIRURGICAL DU CANCER DU RECTUM. By François d'Allaines, with the collaboration of A. Le Roy and Ch. Dubost. Paris: Editions Medicales Flammarion, 1946.

the rectal sphincters. He states that one should always remove 15 centimeters of bowel above the tumor and 5 centimeters below. If this can be done and the rectal sphincter preserved, well and good; if not, the sphincter must be sacrificed. He favors as a routine standard procedure the abdominal plus the sacral route with preservation of the sphincter. This operation requires more time, is more precise, and often is followed by fistulas as compared with the abdominoperineal operation in which the sphincter is sacrificed but which practically never is followed by fistulas.

The work is illustrated by excellent drawings of all the crucial steps in the operative procedures. The author belongs to the group of surgeons who advocate a wide exposure. If one wishes to avoid a structure, one makes a generous incision, exposes it, and identifies it. This procedure is advocated for the ureter, vas, bladder, prostate, vagina, seminal vesicles, and uterus. He also advises that if any of these structures are adherent to the tumor mass, they in whole or in part, should be removed *en bloc* with the tumor.

In discussing the preservation of the sphincters by preservation and anastomosis or by removal of the anal mucosa and drawing the bowel through the sphincter, he states that the "pull through" technique gives an imperfect sphincter that rarely holds liquids or gas, but does hold solids. He believes that an abdominal colostomy is preferable to a perineal one, contrary to the opinion of some American surgeons.

To everyone interested in the carcinoma of the rectum, this book should prove of great interest. It is written by a surgeon of wide experience who reviews and analyzes all the recent world literature on the subject.

VICTOIRE LESPINASSE.

AN entirely new approach to the science of conduction anesthesia is presented in Pitkin's volume entitled *Conduction Anesthesia*.[1] Such a complete coverage of the subject is to be found in no other single volume. The book is edited by Southworth and Hingson, and there are eight collaborators It contains the author's personal approach to the science, authenticated by years of practical application, and a coverage of closely allied developments by well-known collaborators. Throughout, a direct application of a knowledge of anatomy and pharmacology to conduction anesthesia is emphasized and the subject matter is presented in as simple a manner as is possible. The author states, "Block anesthesia is neither complicated nor difficult. . . . Anyone who is familiar with the pharmacology of local anesthetic drugs and with osseous and neuro-anatomy can become a proficient local anesthetist in a very short time." He elucidates a number of fallacies in local anesthesia which have been perpetuated from the time of early workers in this field. Crile's work in local anesthesia, he states, was his incentive and the practice of Crile's methods made his work possible. The text is intended as a guide to the more common procedures employed by the average physician as well as a source of technical information for those interested in specialized fields of surgery.

The anatomy of the cranial and spinal nerves and the autonomic nervous system is completely discussed. The entire nerve supply of various organs of the body is given under a separate heading for each organ. This subject matter is arranged so that easy reference is possible when needed. The concept is stressed that the autonomic as well as somatic pathways must be blocked for successful anesthesia. The underlying principles of conduction anesthesia are elaborated and specific techniques are given in detail. There is a section on the pharmacology and toxicology of local anesthetics. The section on shock contains a basic review and a discussion of the most recent and controversial concepts of this syndrome. Directions for and discussion of the various methods of blocking all parts of the body occupy 426 pages. The author makes it clear that he prefers the simplest method when the desired result may be obtained by this means.

There is no area of the body and few combinations of complicating factors which have not been considered. Easy reference may be made to any specific nerve block desired and in each instance complete directions are given. Repetition of anatomical descriptions and techniques of injection is frequently purposefully included so that all pertinent information is present under each heading without referring the reader to previous or subsequent pages.

Sections on spinal and continuous spinal anesthesia follow. Applicable knowledge of anatomy and pharmacology, variations in techniques, and complications are discussed. Because effects may be controlled the method is applicable to a wide variety of conditions. Ability to withdraw the dose is stressed as a safety factor in reference to the continuous spinal technique. The section on refrigeration anesthesia contains modern concepts of the physiological changes incident to reduction of temperature and application to operative procedures. Methods to be used are elucidated. There is a section on therapeutic nerve block which covers the various conditions in which this method of treatment may be of value.

The excellent illustrations and drawings are perhaps the outstanding feature of the book. They are numerous, and clearly illustrate every phase of the techniques described. The volume will have a widespread appeal to anesthesiologists and surgeons. The ready availability of its subject matter and completeness of coverage make it an unsurpassed reference text. The editors and collaborators are to be congratulated upon the compilation of this excellent work. We regret that Dr. Pitkin is no longer with us to receive well deserved acclaim.

WILLIAMS E. PEMBLETON.
RALPH M. TOVELL.

[1] CONDUCTION ANESTHESIA. Clinical Studies of George P. Pitkin, M.D., F.A.C.S., F.I.C.A. Edited by James L. Southworth, M.D., and Robert A. Hingson, M.D. Philadelphia, London, Montreal: J. B. Lippincott Co., 1946.

THE monograph entitled *Endocrine Function of the Hypophysis*[1], reprinted from the set *Oxford Loose-Leaf Medicine*, is a compact, terse, yet complete treatise on a subject which still, in spite of the extensive study which has been carried out on the functions of the pituitary gland, remains incompletely explored and a matter for contention among investigators. The author, a well known clinical endocrinologist and research worker in the field of endocrinology, has obviously accomplished a rather heroic success in sweeping together and co-ordinating up to the present day all the pertinent data concerning the form and functions of the hypophysis.

The book is divided into five parts: (1) anatomy, embryology and phylogeny of the hypophysis cerebri; (2) cytophysiology and biochemistry of the adenohypophysis; (3) biological, biochemical, physiological and genetic concepts of growth; (4) clinical disorders of growth; and (5) cytophysiology, biochemistry and pharmacology of the neurohypophysis. Each of these sections is furnished with an exhaustive bibliography which reaches from the present day back into the early investigations of the past century, thus providing for the serious student of this particular study a valuable source material.

[1]ENDOCRINE FUNCTION OF THE HYPOPHYSIS. By Harry B. Friedgood, M.D. Reprinted from *Oxford Loose-Leaf Medicine*. Edited by Henry A. Christian, A.M., M.D., LL.D., Sc.D. (Hon.), F.A.C.P., Hon. F.R.C.P. (Can.). New York: Oxford University Press, 1946.

The section on anatomy and embryology of the gland is one of the best to be found in English print, being written in an authoritative and scholarly manner to lead up to the facts concerning the physiology of the organ which is described later. The section on clinical disorders treats briefly but adequately, and with good illustrations, of the various clinical syndromes which follow disease of the hypophysis. The paragraphs on dwarfism are gratifying in that the subject is handled so as to leave the reader with the feeling that he has just read about a *new* subject. In this, as in most of the other parts of the book, the writer's style is direct and factual, yet never laborious or hackneyed.

With the background of information relative to the anatomy and physiology of the entire organ, the author has been able clearly to show the pharmacologic and clinical applications of this knowledge for the distinctly two separate parts of the gland, the adenohypophysis and the neurohypophysis. If the average medical school student or doctor is not entirely clear on the individual functions of these two actually separate organs, and is not entirely certain of the rational application of the commercial biological preparations of the gland, he has but to review this monograph. It is not fast or easy reading, but it is stimulating and informative. After reading it one feels that "that is just about all there is to the subject."

JOHN MARTIN.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return or the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

THE ANATOMY OF THE BRONCHIAL TREE. By R. C. Brock, M.S. (Lond.), F.R.C.S. (Eng.). London, New York, Toronto: Geoffrey Cumberlege, Oxford University Press, 1946.

THE ESSENTIALS OF OBSTETRICS AND GYNECOLOGY. By William Albert Scott, B.A., M.B., F.R.C.S. (Can.), F.R.C.O.G. (Eng.), and H. Brookfield Van Wyck, B.A., M.B., F.R.C.S. (Can.), F.R.C.O.G. (Eng.). Philadelphia: Lea & Febiger, 1946.

ENCYCLOPEDIA OF ENDOCRINOLOGY. By Hans Selye, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada). Sect. IV. The Ovary. Vol. VII. Ovarian Tumors. Sect. IV. The Ovary. Vol. VII. Bibl. Ovarian Tumors (Bibliography). Montreal: Richardson, Bond and Wright, 1946.

DA CONSERVACÃO DOS OVÁRIOS NAS HISTERECTOMIAS. By Angelo de Abreu e Lima. Recife, 1946.

AN INTEGRATED PRACTICE OF MEDICINE. By Harold Thomas Hyman, M.D. Vols. I, II, III, and IV, and Index. Philadelphia and London: W. B. Saunders Co., 1947.

THE COMPLEAT PEDIATRICIAN. By Wilburt C. Davidson, M.A., D.Sc., M.D. Durham, N. C.: Duke University Press, 1946.

PENICILLIN IN NEUROLOGY. By. A. Earl Walker, M.D. and Herbert C. Johnson, M.D. Springfield, Ill.: Charles C. Thomas, 1946.

SIGNIFICANCE OF THE EXTRACELLULAR FLUID IN CLINICAL MEDICINE. By L. H. Newburgh, M.D. Ann Arbor, Michigan: J. W. Edwards, Inc., 1946.

PARENTAL ALIMENTATION IN SURGERY WITH SPECIAL REFERENCE TO PROTEINS AND AMINO ACIDS. By Robert Elman, M.D. New York, London: Paul B. Hoeber, 1947.

CARDIOVASCULAR DISEASES. By David Scherf, M.D., F.A.C.P., and Linn J. Boyd, M.D., F.A.C.P. Philadelphia, London, Montreal: J. B. Lippincott Co., 1947.

GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY WITH CLINICAL AND ENDOCRINE RELATIONS. By Emil Novak, A.B., M.D., D.Sc. (Hon. Dublin), F.A.C.S. Philadelphia and London: W. B. Saunders Co., 1947.

FURTHER STUDIES IN ENCEPHALOGRAPHY. By E. Graeme Robertson, M.D. (Melb.), F.R.C.P., F.R.A.C.P. Melbourne: Macmillan & Co., Ltd., 1946.

TRATAMIENTO MEDICO DE LA ULCERA GASTRODUODENAL EXPERIMENTAL. By Dr. Juan Nasio. Buenos Aires: La Prensa Medica Argentina, 1946.

LA VIDA DE LOS MEDICOS EN MEXICO. By Conrado Zuckermann. Mexico: Ediciones Minerva, 1945.

OFFICE ENDOCRINOLOGY. By Robert B. Greenblatt, B.A., M.D., C.M. 3d ed. Springfield, Ill.: Charles C. Thomas, 1947.

THE monograph entitled *Endocrine Function of the Hypophysis*[1], reprinted from the set *Oxford Loose-Leaf Medicine*, is a compact, terse, yet complete treatise on a subject which still, in spite of the extensive study which has been carried out on the functions of the pituitary gland, remains incompletely explored and a matter for contention among investigators. The author, a well known clinical endocrinologist and research worker in the field of endocrinology, has obviously accomplished a rather heroic success in sweeping together and co-ordinating up to the present day all the pertinent data concerning the form and functions of the hypophysis.

The book is divided into five parts: (1) anatomy, embryology and phylogeny of the hypophysis cerebri; (2) cytophysiology and biochemistry of the adenohypophysis; (3) biological, biochemical, physiological and genetic concepts of growth; (4) clinical disorders of growth; and (5) cytophysiology, biochemistry and pharmacology of the neurohypophysis. Each of these sections is furnished with an exhaustive bibliography which reaches from the present day back into the early investigations of the past century, thus providing for the serious student of this particular study a valuable source material.

[1]ENDOCRINE FUNCTION OF THE HYPOPHYSIS. By Harry B. Friedgood, M.D. Reprinted from *Oxford Loose-Leaf Medicine*. Edited by Henry A. Christian, A.M., M.D., LL.D., Sc.D. (Hon.), F.A.C.P., Hon. F.R.C.P. (Can.). New York: Oxford University Press, 1946.

The section on anatomy and embryology of the gland is one of the best to be found in English print, being written in an authoritative and scholarly manner to lead up to the facts concerning the physiology of the organ which is described later. The section on clinical disorders treats briefly but adequately, and with good illustrations, of the various clinical syndromes which follow disease of the hypophysis. The paragraphs on dwarfism are gratifying in that the subject is handled so as to leave the reader with the feeling that he has just read about a *new* subject. In this, as in most of the other parts of the book, the writer's style is direct and factual, yet never laborious or hackneyed.

With the background of information relative to the anatomy and physiology of the entire organ, the author has been able clearly to show the pharmacologic and clinical applications of this knowledge for the distinctly two separate parts of the gland, the adenohypophysis and the neurohypophysis. If the average medical school student or doctor is not entirely clear on the individual functions of these two actually separate organs, and is not entirely certain of the rational application of the commercial biological preparations of the gland, he has but to review this monograph. It is not fast or easy reading, but it is stimulating and informative. After reading it one feels that "that is just about all there is to the subject."

JOHN MARTIN.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return or the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

THE ANATOMY OF THE BRONCHIAL TREE. By R. C. Brock, M.S. (Lond.), F.R.C.S. (Eng.). London, New York, Toronto: Geoffrey Cumberlege, Oxford University Press, 1946.

THE ESSENTIALS OF OBSTETRICS AND GYNECOLOGY. By William Albert Scott, B.A., M.B., F.R.C.S. (Can.), F.R.C.O.G. (Eng.), and H. Brookfield Van Wyck, B.A., M.B., F.R.C.S. (Can.), F.R.C.O.G. (Eng.). Philadelphia: Lea & Febiger, 1946.

ENCYCLOPEDIA OF ENDOCRINOLOGY. By Hans Selye, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada). Sect. IV. The Ovary. Vol. VII. Ovarian Tumors. Sect. IV. The Ovary. Vol. VII. Bibl. Ovarian Tumors (Bibliography). Montreal: Richardson, Bond and Wright, 1946.

DA CONSERVACÃO DOS OVÁRIOS NAS HISTERECTOMIAS. By Angelo de Abreu e Lima. Recife, 1946.

AN INTEGRATED PRACTICE OF MEDICINE. By Harold Thomas Hyman, M.D. Vols. I, II, III, and IV, and Index. Philadelphia and London: W. B. Saunders Co., 1947.

THE COMPLEAT PEDIATRICIAN. By Wilburt C. Davidson, M.A., D.Sc., M.D. Durham, N. C.: Duke University Press, 1946.

PENICILLIN IN NEUROLOGY. By. A. Earl Walker, M.D. and Herbert C. Johnson, M.D. Springfield, Ill.: Charles C. Thomas, 1946.

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